09/889,904

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=> d his

     (FILE 'HOME' ENTERED AT 22:27:30 ON 16 DEC 2001)

     FILE 'CAPLUS' ENTERED AT 22:27:47 ON 16 DEC 2001
L1            71 S (NK(2A)3 OR NEUROKININ(2A)3)(4A)(ANTAGONIST# OR INHIBITOR#)
L2             0 S L1 AND HYPERANDROGEN?
L3             2 S L1 AND (TESTOSTERONE OR LH OR LUTEINIZING(2A)HORMONE)(P)(INHI
L4          2652 S ANTI(2A)ANDROGEN# OR ANTIANDROGEN#
L5         20772 S (ACNE OR HIRSUTISM OR TESTICULAR(4A)CANCER OR PROSTAT?(3A)CAN
L6           735 S L4 AND L5
L7           605 S L4(P)L5
L8           448 S (ANTIANDROGEN OR ANTI(2A)ANDROGEN) (P) (ACNE OR HIRSUTISM OR
L9           228 S L8 AND PY<1998

     FILE 'STNGUIDE' ENTERED AT 22:57:18 ON 16 DEC 2001

     FILE 'CAPLUS' ENTERED AT 22:57:53 ON 16 DEC 2001

     FILE 'STNGUIDE' ENTERED AT 23:02:44 ON 16 DEC 2001

     FILE 'CAPLUS' ENTERED AT 23:05:46 ON 16 DEC 2001
L10           30 S L9 AND TESTOSTERONE AND (LH OR LUTEINIZING(2A)HORMONE)
L11        12743 S (SUPPRESS? OR INHIBIT? OR PREVENT?)(P)TESTOSTERONE
L12           71 S (NK(2A)3 OR NEUROKININ(2A)3)(4A)(ANTAGONIST# OR INHIBITOR#)
L13            1 S L11 AND L12
L14          653 S L11 AND (ANTIANDROGEN# OR ANTI(2A)ANDROGEN#)
L15          474 S L11 (P) (ANTIANDROGEN# OR ANTI(2A)ANDROGEN#)
L16          381 S L15 AND PY<1998

     FILE 'STNGUIDE' ENTERED AT 23:47:25 ON 16 DEC 2001
L17            0 S (SUPPRESS? OR INHIBIT? OR PREVENT?)(P)(LH OR LUTEINIZING(2A)H

     FILE 'CAPLUS' ENTERED AT 23:57:55 ON 16 DEC 2001
L18         7554 S (SUPPRESS? OR INHIBIT? OR PREVENT?)(P)(LH OR LUTEINIZING(2A)H
L19           71 S (NK(2A)3 OR NEUROKININ(2A)3)(4A)(ANTAGONIST# OR INHIBITOR#)
L20            0 S L18 AND L19

     FILE 'STNGUIDE' ENTERED AT 23:58:41 ON 16 DEC 2001

=>
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=> s l9 and testosterone and (LH or luteinizing(2a)hormone)
         49307 TESTOSTERONE
         49982 LH
         12507 LUTEINIZING
        225307 HORMONE
         12020 LUTEINIZING(2A)HORMONE
L10         30 L9 AND TESTOSTERONE AND (LH OR LUTEINIZING(2A)HORMONE)

=> d l10 abs ibib kwic 1-30

L10  ANSWER 1 OF 30  CAPLUS  COPYRIGHT 2001 ACS
AB   A review with 34 refs.  The optimal treatment for many unresectable solid
     tumors involves the combined use of chemotherapy and radiation.
     Retrospective and prospective randomized trials demonstrating a redn. in
     failure rates when neoadjuvant androgen suppression is combined with
     radiotherapy suggest that this is also likely to be true for prostate
     cancer.  The absence of overlapping toxicities, the high response rates to
     androgen suppression, and the ease with which the prostate is included in
     radiotherapy portals makes the prostate an ideal site for chemoradiation.
     Since radiation and hormonally mediated apoptosis appear to be induced by
     different mechanisms their interaction may well be synergistic.
     Volumetric changes induced by hormonal suppression facilitate radioactive
     implantation in the prostate in men with large glands.  This neoadjuvant
     approach also reduces the amt. of normal tissue to be irradiated when used
     prior to 3-dimensional conformal radiotherapy while allowing higher doses
     to the tumor.  It may be particularly important to use antiandrogens to
     block the "intraprostatic flare" that may result from the
     testosterone surge induced by LH-releasing hormone in
     patients undergoing neoadjuvant (short course) androgen suppression.  Men
     who are at particularly "high risk" for biochem. failure when treated with
     radiotherapy alone should probably receive a "longer" course of complete
     neoadjuvant and possibly adjuvant hormonal blockade, but the optimal
     duration and sequence of androgen suppression remain to be defined.
ACCESSION NUMBER:         1998:544505  CAPLUS
DOCUMENT NUMBER:          129:298419
TITLE:                    Neoadjuvant therapy prior to radiotherapy for
                          clinically localized prostate cancer
AUTHOR(S):                Roach, Mack, III
CORPORATE SOURCE:         Radiation and Medical Oncology, University of
                          California, San Francisco, CA, 94143-0226, USA
SOURCE:                   Eur. Urol. (1997), 32(Suppl. 3, Management
                          of Prostate Cancer), 48-54
                          CODEN: EUURAV; ISSN: 0302-2838
PUBLISHER:                S. Karger AG
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
SO   Eur. Urol. (1997), 32(Suppl. 3, Management of Prostate Cancer),
     48-54
     CODEN: EUURAV; ISSN: 0302-2838
AB   A review with 34 refs.  The optimal treatment for many unresectable solid
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     Retrospective and prospective randomized trials demonstrating a redn. in
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     radiotherapy suggest that this is also likely to be true for prostate
     cancer.  The absence of overlapping toxicities, the high response rates to
     androgen suppression, and the ease with which the prostate is included in
     radiotherapy portals makes the prostate an ideal site for chemoradiation.
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Since radiation and hormonally mediated apoptosis appear to be induced by different mechanisms their interaction may well be synergistic. Volumetric changes induced by hormonal suppression facilitate radioactive implantation in the prostate in men with large glands. This neoadjuvant approach also reduces the amt. of normal tissue to be irradiated when used prior to 3-dimensional conformal radiotherapy while allowing higher doses to the tumor. It may be particularly important to use antiandrogens to block the "intraprostatic flare" that may result from the **testosterone** surge induced by **LH**-releasing hormone in patients undergoing neoadjuvant (short course) androgen suppression. Men who are at particularly "high risk" for biochem. failure when treated with radiotherapy alone should probably receive a "longer" course of complete neoadjuvant and possibly adjuvant hormonal blockade, but the optimal duration and sequence of androgen suppression remain to be defined.

ST review neoadjuvant **antiandrogen** radiotherapy **prostate cancer**

IT Prostatic tumor inhibitors
Radiotherapy
(neoadjuvant **antiandrogen** treatment prior to radiotherapy for humans **prostate cancer**)

IT Antiandrogens
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neoadjuvant **antiandrogen** treatment prior to radiotherapy for humans **prostate cancer**)

L10 ANSWER 2 OF 30 CAPLUS COPYRIGHT 2001 ACS

AB A review, with 73 refs. Leuprorelin has demonstrated effectiveness comparable to orchiectomy and oral diethylstilbestrol for the palliation of advanced **prostate cancer**. Unlike orchiectomy, leuprorelin's effects are reversible also leuprorelin is not assocd. with the cardiovascular or thromboembolic adverse effects of estrogens. For these reasons, leuprorelin has been widely used as an alternative to surgical castration or to estrogens in the treatment of metastatic **prostate cancer**. Sustained-release leuprorelin microsphere formulations have been developed which exhibit zero order release of active drug from the injection site, such that in the United States the 7.5 mg dosage strength is recommended to be administered once a month and the 22.5 mg dosage strength once every three months. Although most patients will have suppressed release of pituitary **LH** by the third or fourth week after the first dose of depot leuprorelin, 4-5% of treated patients have been reported to have delayed responses, taking many more weeks or months to respond. A transient biochem. hormone escape has also been reported, although worsening of clin. symptoms has not accompanied the elevation of serum **testosterone** levels during treatment. Usually, leuprorelin is initiated as monotherapy when patients with advanced **prostate cancer** become symptomatic. However, newer studies of combination therapy of **LH** releasing hormone analogs with antiandrogens suggest that early initiation of therapy, at the time of diagnosis of advanced disease, may be beneficial, particularly in a subgroup of patients with small vol. disease and good performance status. Leuprorelin is also undergoing evaluation as neoadjuvant therapy prior to radical **prostatectomy** for localized **prostate cancer**. Preliminary studies suggest that neoadjuvant leuprorelin in combination with an **antiandrogen** may be effective in downstaging prostate tumors. Leuprorelin commonly produces several adverse effects: hot flashes, decreased libido and

impotence, and tumor flare.

ACCESSION NUMBER: 1997:707012 CAPLUS
DOCUMENT NUMBER: 128:26771
TITLE: Therapeutic effects of leuprorelin microspheres in prostate cancer
AUTHOR(S): Sharifi, Roohollah; Ratanawong, Chirasakdi; Jung, Ashley; Wu, Zhi; Browneller, Robert; Lee, Mary
CORPORATE SOURCE: FACS, University of Illinois at Chicago, 833 South Wood Street, room 132-CSB (m/c 907), Chicago, USA
SOURCE: Adv. Drug Delivery Rev. (**1997**), 28(1), 121-138
CODEN: ADDREP; ISSN: 0169-409X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
SO Adv. Drug Delivery Rev. (**1997**), 28(1), 121-138
CODEN: ADDREP; ISSN: 0169-409X
AB A review, with 73 refs. Leuprorelin has demonstrated effectiveness comparable to orchiectomy and oral diethylstilbestrol for the palliation of advanced **prostate cancer**. Unlike orchiectomy, leuprorelin's effects are reversible also leuprorelin is not assocd. with the cardiovascular or thromboembolic adverse effects of estrogens. For these reasons, leuprorelin has been widely used as an alternative to surgical castration or to estrogens in the treatment of metastatic **prostate cancer**. Sustained-release leuprorelin microsphere formulations have been developed which exhibit zero order release of active drug from the injection site, such that in the United States the 7.5 mg dosage strength is recommended to be administered once a month and the 22.5 mg dosage strength once every three months. Although most patients will have suppressed release of pituitary **LH** by the third or fourth week after the first dose of depot leuprorelin, 4-5% of treated patients have been reported to have delayed responses, taking many more weeks or months to respond. A transient biochem. hormone escape has also been reported, although worsening of clin. symptoms has not accompanied the elevation of serum **testosterone** levels during treatment. Usually, leuprorelin is initiated as monotherapy when patients with advanced **prostate cancer** become symptomatic. However, newer studies of combination therapy of **LH** releasing hormone analogs with antiandrogens suggest that early initiation of therapy, at the time of diagnosis of advanced disease, may be beneficial, particularly in a subgroup of patients with small vol. disease and good performance status. Leuprorelin is also undergoing evaluation as neoadjuvant therapy prior to radical **prostatectomy** for localized **prostate cancer**. Preliminary studies suggest that neoadjuvant leuprorelin in combination with an **antiandrogen** may be effective in downstaging prostate tumors. Leuprorelin commonly produces several adverse effects: hot flashes, decreased libido and impotence, and tumor flare.
IT 9034-40-6D, **LH**-RH, analogs 53714-56-0, Leuprorelin
RL: BAC (Biological activity or effector, except adverse); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(leuprorelin microspheres in treatment of prostate cancer)

L10 ANSWER 3 OF 30 CAPLUS COPYRIGHT 2001 ACS
AB Nonsteroidal **antiandrogen** casodex and steroidal **antiandrogen** epitestosterone were administered to intact male mice, and their effect on femoral bones and circulating calcium,

phosphate, **testosterone**, and **LH** were compared with controls and castrated animals. Pure **antiandrogen** casodex in a dose used in humans for treatment of **prostate cancer** decreased the wt. of seminal vesicles, organ which is highly sensitive to the androgenic effect, increased insignificantly the concn. of **LH** and of **testosterone**, but did not have any effect on bone d. or mineral content of bone. Epitestosterone, which not only inhibits the binding of androgens to their receptors but also inhibits the formation of dihydrotestosterone from **testosterone**, and is reported to interfere with aromatization of **testosterone** to estrogens, decreased the bone d., ash wt., and calcium and phosphate content of femoral bone tissue significantly, although not to values as low as those seen in castrated animals.

ACCESSION NUMBER: 1997:349194 CAPLUS
DOCUMENT NUMBER: 127:45153
TITLE: Effect of antiandrogens casodex and epitestosterone on bone composition in mice
AUTHOR(S): Broulik, P. D.; Starka, L.
CORPORATE SOURCE: Third Medical Clinic First Medical Faculty, Charles University, Prague, Czech Rep.
SOURCE: Bone (N. Y.) (**1997**), 20(5), 473-475
CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

SO Bone (N. Y.) (**1997**), 20(5), 473-475
CODEN: BONEDL; ISSN: 8756-3282

AB Nonsteroidal **antiandrogen** casodex and steroidal **antiandrogen** epitestosterone were administered to intact male mice, and their effect on femoral bones and circulating calcium, phosphate, **testosterone**, and **LH** were compared with controls and castrated animals. Pure **antiandrogen** casodex in a dose used in humans for treatment of **prostate cancer** decreased the wt. of seminal vesicles, organ which is highly sensitive to the androgenic effect, increased insignificantly the concn. of **LH** and of **testosterone**, but did not have any effect on bone d. or mineral content of bone. Epitestosterone, which not only inhibits the binding of androgens to their receptors but also inhibits the formation of dihydrotestosterone from **testosterone**, and is reported to interfere with aromatization of **testosterone** to estrogens, decreased the bone d., ash wt., and calcium and phosphate content of femoral bone tissue significantly, although not to values as low as those seen in castrated animals.

IT 58-22-0, **Testosterone** 7440-70-2, Calcium, biological studies
9002-67-9, **LH** 14265-44-2, Phosphate, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(effect of antiandrogens casodex and epitestosterone on bone compn. in mice)

L10 ANSWER 4 OF 30 CAPLUS COPYRIGHT 2001 ACS

AB Administration of 4 mg of antiprogestagen RU486 to 4-day-cyclic rats over 8 consecutive days starting on the day of estrus (Day 1) induced an **anovulatory** cystic ovarian condition with endocrine and morphol. features similar to those exhibited in polycystic ovarian disease (PCO). To det. whether the RU486-treated rat responds in an analogous fashion to therapies similar to those that have been used to treat human PCO, RU486-treated rats were injected on Days 5 and 7 with (1) 1 mg of an LHRH antagonist (**LH**-RHa), (2) 5 IU of human FSH (hFSH), (3) 2 mg of

the **antiandrogen** flutamide (FLU), (4) 1 mg of the antiestrogen tamoxifen (TMX) or (5) 1 mg of the dopamine agonist bromocriptine (BRC). Controls were intact cyclic rats decapitated on estrus and rats injected with RU486 and the corresponding vehicles (saline or 70% ethanol) used with LHRHa, hFSH, FLU, TMX, and BRC injections. RU486-treated rats were decapitated on Day 9, and the serum concns. of **LH**, FSH, prolactin (PRL), **testosterone** (T), and estradiol-17.beta. (E2) were detd. Pituitary and ovary wt., no. of follicular cysts, size of the corpora lutea, and rates of follicular growth and **atresia** were also noted. Finally, the ovulatory response to ovine **LH** (oLH) in rats treated with RU486 and injected with various doses of hFSH (5, 10, or 20 IU) was evaluated. While administration of LHRHa and of TMX decreased the serum concns. of **LH**, T, and E2 and the **LH** /FSH and T/E2 ratios, and injections of BRC and of FLU increased the serum concns. of **LH** and T, the administration of hFSH (10 IU) to RU486-treated rats increased only the serum levels of E2. All treatments decreased, though in different degrees, both the no. of cysts and the rate of follicular **atresia**, and stimulated follicular growth. The pos. effects on follicular growth and **atresia** were significantly higher in those rats injected with hFSH. Moreover, RU486-treated rats injected with different doses of hFSH ovulated in a dose-dependent manner in response to oLH. Rats deprived of the actions of progesterone through the administration of the antiprogestagen RU486 had (1) endocrine and morphol. alterations comparable to those obsd. in women with PCO, (2) analogous responses to therapies similar to those that have been used to treat human PCO, and (3) an ovulatory response to combined treatment with FSH and **LH**. These results establish the fundamental adequacy of using the RU486-treated rat as a PCO model.

ACCESSION NUMBER: 1997:49040 CAPLUS
DOCUMENT NUMBER: 126:127092
TITLE: RU486-treated rats show endocrine and morphological responses to therapies analogous to responses of women with polycystic ovary syndrome treated with similar therapies
AUTHOR(S): Ruiz, Antonio; Aguilar, Rafaela; Tebar, Maria; Gaytan, Francisco; Sanchez-Criado, Jose E.
CORPORATE SOURCE: Faculty Medicine, Univ. Cordoba, Cordoba, 14004, Spain
SOURCE: Biol. Reprod. (**1996**), 55(6), 1284-1291
CODEN: BIREBV; ISSN: 0006-3363
PUBLISHER: Society for the Study of Reproduction
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Biol. Reprod. (**1996**), 55(6), 1284-1291
CODEN: BIREBV; ISSN: 0006-3363
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prolactin (PRL), **testosterone** (T), and estradiol-17.beta. (E2) were detd. Pituitary and ovary wt., no. of follicular cysts, size of the corpora lutea, and rates of follicular growth and **atresia** were also noted. Finally, the ovulatory response to ovine **LH** (oLH) in rats treated with RU486 and injected with various doses of hFSH (5, 10, or 20 IU) was evaluated. While administration of LHRHa and of TMX decreased the serum concns. of **LH**, T, and E2 and the **LH** /FSH and T/E2 ratios, and injections of BRC and of FLU increased the serum concns. of **LH** and T, the administration of hFSH (10 IU) to RU486-treated rats increased only the serum levels of E2. All treatments decreased, though in different degrees, both the no. of cysts and the rate of follicular **atresia**, and stimulated follicular growth. The pos. effects on follicular growth and **atresia** were significantly higher in those rats injected with hFSH. Moreover, RU486-treated rats injected with different doses of hFSH ovulated in a dose-dependent manner in response to oLH. Rats deprived of the actions of progesterone through the administration of the antiprogestagen RU486 had (1) endocrine and morphol. alterations comparable to those obsd. in women with PCO, (2) analogous responses to therapies similar to those that have been used to treat human PCO, and (3) an ovulatory response to combined treatment with FSH and **LH**. These results establish the fundamental adequacy of using the RU486-treated rat as a PCO model.

IT 50-28-2, Estradiol, biological studies 57-83-0, Progesterone, biological studies 58-22-0, **Testosterone** 9002-62-4, Prolactin, biological studies 9002-67-9, **LH**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(RU486-treated rats show endocrine and morphol. responses to therapies analogous to responses of women with polycystic ovary syndrome treated with similar therapies)

L10 ANSWER 5 OF 30 CAPLUS COPYRIGHT 2001 ACS

AB A review with .apprx.155 refs. An LHRH agonist was first administered to a **prostate cancer** patient 16 yr ago in 1980 while combination therapy with an LHRH agonist and a pure **antiandrogen** was first administered 14 yr ago in 1982. The authors take this opportunity to review briefly the events which, in the authors' opinion, led to such fundamental changes in the endocrine therapy of **prostate cancer**. Following the observations of Huggins and his colleagues in 1941, orchiectomy and treatment with high doses of estrogens remained the std. therapy of **prostate cancer** for 50 yr. Discovery of the structure of LHRH in 1971 by Schally and his colleagues stimulated the synthesis of highly potent analogs of LHRH with the objective of treating **infertility**. However, difficulties were met in finding the proper schedule of administration as well as the dose of LHRH agonists which could maintain stimulatory effects upon repeated administration. In fact, contrary to the expectations of a stimulatory effect, the authors found in 1977 that treatment of adult male rats with an LHRH agonist for a few days caused some inhibition of ventral prostate and seminal vesicle wt., although the inhibitory effects achieved were small compared with those of castration. It was then believed that the high serum **LH** levels induced by LHRH agonist treatment caused desensitization of the steroidogenic response in the testes. Even more unexpected was the finding that of all the species studied, man was the most sensitive to the inhibitory action of LHRH agonists on testicular androgen biosynthesis and that medical castration could be easily achieved with LHRH agonists in adult men. In fact, a single intranasal administration of an LHRH agonist to healthy men in 1979 caused the expected acute rise in serum levels of **testosterone** and its

precursors. This increase, however, was followed by a loss of diurnal cyclicity and lowered serum androgen levels which lasted for 3 to 4 days, thus suggesting that man is exquisitely sensitive to the inhibitory action of LHRH agonists. When, in 1980, the first **prostate cancer** patient received an LHRH agonist at the Laval University Medical Center, it was found that treatment with a high dose of the peptide caused a dramatic redn. in serum **testosterone** and dihydrotestosterone (DHT) after 2 wk of administration.

ACCESSION NUMBER: 1996:703646 CAPLUS
DOCUMENT NUMBER: 125:317533
TITLE: History of LHRH agonist and combination therapy in prostate cancer
AUTHOR(S): Labrie, F.; Belanger, A.; Cusan, L.; Labrie, C.; Simard, J.; Luu-The, V.; Diamond, P.; Gomez, J-L.; Candas, B.
CORPORATE SOURCE: Le Centre Hospitalier, Universitaire de Quebec, Quebec, PQ, G1V 4G2, Can.
SOURCE: Endocr.-Relat. Cancer (**1996**), 3(3), 243-278
CODEN: ERCAE9; ISSN: 1351-0088
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
SO Endocr.-Relat. Cancer (**1996**), 3(3), 243-278
CODEN: ERCAE9; ISSN: 1351-0088
AB A review with .apprx.155 refs. An LHRH agonist was first administered to a **prostate cancer** patient 16 yr ago in 1980 while combination therapy with an LHRH agonist and a pure **antiandrogen** was first administered 14 yr ago in 1982. The authors take this opportunity to review briefly the events which, in the authors' opinion, led to such fundamental changes in the endocrine therapy of **prostate cancer**. Following the observations of Huggins and his colleagues in 1941, orchiectomy and treatment with high doses of estrogens remained the std. therapy of **prostate cancer** for 50 yr. Discovery of the structure of LHRH in 1971 by Schally and his colleagues stimulated the synthesis of highly potent analogs of LHRH with the objective of treating **infertility**. However, difficulties were met in finding the proper schedule of administration as well as the dose of LHRH agonists which could maintain stimulatory effects upon repeated administration. In fact, contrary to the expectations of a stimulatory effect, the authors found in 1977 that treatment of adult male rats with an LHRH agonist for a few days caused some inhibition of ventral prostate and seminal vesicle wt., although the inhibitory effects achieved were small compared with those of castration. It was then believed that the high serum **LH** levels induced by LHRH agonist treatment caused desensitization of the steroidogenic response in the testes. Even more unexpected was the finding that of all the species studied, man was the most sensitive to the inhibitory action of LHRH agonists on testicular androgen biosynthesis and that medical castration could be easily achieved with LHRH agonists in adult men. In fact, a single intranasal administration of an LHRH agonist to healthy men in 1979 caused the expected acute rise in serum levels of **testosterone** and its precursors. This increase, however, was followed by a loss of diurnal cyclicity and lowered serum androgen levels which lasted for 3 to 4 days, thus suggesting that man is exquisitely sensitive to the inhibitory action of LHRH agonists. When, in 1980, the first **prostate cancer** patient received an LHRH agonist at the Laval University Medical Center, it was found that treatment with a high dose of the peptide caused a dramatic redn. in serum **testosterone** and dihydrotestosterone (DHT) after 2 wk of administration.

IT 9034-40-6D, **LH**-RH, agonists
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(history of LHRH agonists and combination therapy in prostate cancer)

L10 ANSWER 6 OF 30 CAPLUS COPYRIGHT 2001 ACS

AB No clear relation between lipoprotein(a) [Lp(a)] and endogenous gonadal hormones has been demonstrated. In this study, we compared the effects on Lp(a) of pharmacol. castration in 50 patients with **prostate cancer** who were undergoing therapy with a gonadotropin-releasing hormone agonist (goserelin), with effects on 58 age-matched controls. We also studied 16 untreated patients under baseline conditions and after 3 mo of therapy with goserelin alone or combined with an **antiandrogen** (flutamide). Neither cross-sectional nor prospective studies showed any significant effects of therapy on Lp(a). However, cluster anal. identified a subgroup of patients showing slight but significant increases in Lp(a) concns., as well as greater declines of **testosterone** and estradiol, suggesting that androgen, like estrogen, can exert some slight, though not easily detectable, influence on Lp(a).

ACCESSION NUMBER: 1996:477529 CAPLUS
DOCUMENT NUMBER: 125:158850
TITLE: Effects of androgen suppression by gonadotropin-releasing hormone agonist and flutamide on lipid metabolism in men with prostate cancer: focus on lipoprotein(a)
AUTHOR(S): Denti, Licia; Pasolini, Giuseppe; Cortellini, Piero; Feratti, Stefania; Sanfellici, Laura; Ablondi, Fabrizio; Valenti, Giorgio
CORPORATE SOURCE: Dep. Geriatrics Urology, Univ. Parma, Parma, Italy
SOURCE: Clin. Chem. (Washington, D. C.) (**1996**), 42(8, Pt. 1), 1176-1181
CODEN: CLCHAU; ISSN: 0009-9147
DOCUMENT TYPE: Journal
LANGUAGE: English

SO Clin. Chem. (Washington, D. C.) (**1996**), 42(8, Pt. 1), 1176-1181
CODEN: CLCHAU; ISSN: 0009-9147

AB No clear relation between lipoprotein(a) [Lp(a)] and endogenous gonadal hormones has been demonstrated. In this study, we compared the effects on Lp(a) of pharmacol. castration in 50 patients with **prostate cancer** who were undergoing therapy with a gonadotropin-releasing hormone agonist (goserelin), with effects on 58 age-matched controls. We also studied 16 untreated patients under baseline conditions and after 3 mo of therapy with goserelin alone or combined with an **antiandrogen** (flutamide). Neither cross-sectional nor prospective studies showed any significant effects of therapy on Lp(a). However, cluster anal. identified a subgroup of patients showing slight but significant increases in Lp(a) concns., as well as greater declines of **testosterone** and estradiol, suggesting that androgen, like estrogen, can exert some slight, though not easily detectable, influence on Lp(a).

ST androgen lipid metab **prostate cancer**; goserelin flutamide lipoprotein a **prostate cancer**; LHRH agonist **antiandrogen** lipoprotein **prostate cancer**

IT Androgens
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(androgen suppression by **LH**-RH agonist and flutamide on lipoprotein(a) in men with prostate cancer)

IT Lipoproteins

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(Lp(a), androgen suppression by **LH**-RH agonist and flutamide on lipoprotein(a) in men with prostate cancer)

IT Prostate gland
(neoplasm, androgen suppression by **LH**-RH agonist and flutamide on lipoprotein(a) in men with prostate cancer)

IT 58-22-0, **Testosterone**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(androgen suppression by **LH**-RH agonist and flutamide on lipoprotein(a) in men with prostate cancer)

IT 13311-84-7, Flutamide 65807-02-5, Goserelin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(androgen suppression by **LH**-RH agonist and flutamide on lipoprotein(a) in men with prostate cancer)

IT 50-28-2, Estradiol, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(estrogen suppression by **LH**-RH agonist and flutamide on lipoprotein(a) in men with prostate cancer)

L10 ANSWER 7 OF 30 CAPLUS COPYRIGHT 2001 ACS

AB Rats treated with the antiprogestagen RU486 (RU) present a cystic ovarian picture compatible endocrinol. and morphol. with the human polycystic ovarian syndrome (PCOS). The administration of an antagonist of LHRH to rats deprived of the actions of progesterone by the antiprogestagen, reduced the high serum levels of **LH**, **testosterone** (T) and estradiol (E2), as well as the quotients **LH**/FSH and T/E2; the ovary decreased in size and presented a lower no. of cysts, a lesser degree of **atresia** and a reactivation of follicular growth. A similar effect was obsd. in the rats treated with the antiestrogen tamoxifen. The administration of the **antiandrogen** flutamide increased the endocrinol. changes, whereas it decreased, in part, the morphol. ones. The redn. in the serum levels of prolactin by the dopaminergic agonist bromocriptine failed to normalize the secretion of gonadotropins and the prodn. of ovarian steroids, although the ovary showed a decrease in the no. of cysts and the degree of **atresia**, as well as an increase in follicular growth. Finally, the administration of human FSH (hFSH) to rats treated with RU increased the peripheral levels of E2 without altering the remaining endocrine parameters. However, hFSH originated an important decrease in the degree of **atresia** and an intense reactivation in follicular growth in the ovary. Similar therapeutic measures used in patients with polycystic ovarian syndrome (PCOS) produce endocrinol. and morphol. changes very like those described above in the rats treated with RU. This, together with the existing similarities between the **anovulatory** cystic picture in the animal model and the patients with PCOS, confirms the value of rats treated with the antiprogestagen RU486 as a model for studying this disease, as well as the importance of progesterone in developing and maintaining the condition of ovarian cysts.

ACCESSION NUMBER: 1995:917233 CAPLUS
DOCUMENT NUMBER: 123:306862
TITLE: Effect of different treatments on hormone secretion and cystic ovarian morphology in the rat treated with RU486
AUTHOR(S): Ruiz, A.; Aguilar, R.; Tebar, M.; Gaytan, F.; Sanchez-Criado, J. E.
CORPORATE SOURCE: Facultad de Medicina, Universidad de Cordoba, 14004, Spain
SOURCE: Endocrinologia (Barcelona) (**1995**), 42(5),

150-5
CODEN: ENDCDP; ISSN: 0211-2299
DOCUMENT TYPE: Journal
LANGUAGE: French
SO Endocrinologia (Barcelona) (**1995**), 42(5), 150-5
CODEN: ENDCDP; ISSN: 0211-2299
AB Rats treated with the antiprogestagen RU486 (RU) present a cystic ovarian picture compatible endocrinol. and morphol. with the human polycystic ovarian syndrome (PCOS). The administration of an antagonist of LHRH to rats deprived of the actions of progesterone by the antiprogestagen, reduced the high serum levels of **LH**, **testosterone** (T) and estradiol (E2), as well as the quotients **LH**/FSH and T/E2; the ovary decreased in size and presented a lower no. of cysts, a lesser degree of **atresia** and a reactivation of follicular growth. A similar effect was obsd. in the rats treated with the antiestrogen tamoxifen. The administration of the **antiandrogen** flutamide increased the endocrinol. changes, whereas it decreased, in part, the morphol. ones. The redn. in the serum levels of prolactin by the dopaminergic agonist bromocriptine failed to normalize the secretion of gonadotropins and the prodn. of ovarian steroids, although the ovary showed a decrease in the no. of cysts and the degree of **atresia**, as well as an increase in follicular growth. Finally, the administration of human FSH (hFSH) to rats treated with RU increased the peripheral levels of E2 without altering the remaining endocrine parameters. However, hFSH originated an important decrease in the degree of **atresia** and an intense reactivation in follicular growth in the ovary. Similar therapeutic measures used in patients with polycystic ovarian syndrome (PCOS) produce endocrinol. and morphol. changes very like those described above in the rats treated with RU. This, together with the existing similarities between the **anovulatory** cystic picture in the animal model and the patients with PCOS, confirms the value of rats treated with the antiprogestagen RU486 as a model for studying this disease, as well as the importance of progesterone in developing and maintaining the condition of ovarian cysts.
IT 9034-40-6, **LH**-RH
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antagonist, effect on hormone secretion and morphol. in polycystic ovary syndrome in rat and human)
IT 50-28-2, Estradiol, biological studies 58-22-0, **Testosterone**
9002-67-9, **LH**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(in blood serum in polycystic ovary syndrome in rat and human in response to hormone therapy)

L10 ANSWER 8 OF 30 CAPLUS COPYRIGHT 2001 ACS
AB The effects of sep. and combined 10-day administration of **antiandrogen** flutamide and hexestrol on the pituitary-gonadal axis and accessory sexual glands were studied in male rats. Hexestrol in a daily dose of 0.002 mg/kg and more prevented the increase of plasma **LH** and **testosterone** (T) levels induced by flutamide (10 mg/kg). The max. (10-fold) decrease of T secretion, compared with the postcastration level, was found in combination of hexestrol (0.04 mg/kg and more) and flutamide (5 or 10 mg/kg). Addnl., .DELTA.5-steroid-3 .beta.-ol dehydrogenase activity in testes was lowered by 24 %. With combined administration of estrogen and **antiandrogen**, an additive suppressive effect was obsd. which was comparable with the effect of castration regarding the wts. of the ventral prostate anterior prostatic lobe and seminal vesicles. The content of fructose in the

tissues of the anterior prostatic lobe dropped abruptly. Total DNA content and the no. of cells in the ventral prostate decreased by 56 % to the postcastration level, though sep. administration of drugs caused no significant changes of these parameters. It is concluded that the antiprostatic effect of low doses of hexestrol in combination with flutamide is provided by antigonadotropic and antiandrogenic effects. This combination is supposed to be reasonable in the treatment of **prostatic cancer**.

ACCESSION NUMBER: 1995:703180 CAPLUS
DOCUMENT NUMBER: 123:276242
TITLE: Inhibiting effect of combined administration of antiandrogen and low dose of estrogen on the pituitary-gonadal axis and prostate in rats
AUTHOR(S): Reznikov, A.G.; Varga, S.V.
CORPORATE SOURCE: Institute of Endocrinology and Metabolism, Kiev, 254114, Ukraine
SOURCE: Endocr. Regul. (**1995**), 29(1), 29-34
CODEN: EREGE3; ISSN: 1210-0668
DOCUMENT TYPE: Journal
LANGUAGE: English

SO Endocr. Regul. (**1995**), 29(1), 29-34
CODEN: EREGE3; ISSN: 1210-0668

AB The effects of sep. and combined 10-day administration of **antiandrogen** flutamide and hexestrol on the pituitary-gonadal axis and accessory sexual glands were studied in male rats. Hexestrol in a daily dose of 0.002 mg/kg and more prevented the increase of plasma **LH** and **testosterone** (T) levels induced by flutamide (10 mg/kg). The max. (10-fold) decrease of T secretion, compared with the postcastration level, was found in combination of hexestrol (0.04 mg/kg and more) and flutamide (5 or 10 mg/kg). Addnl., .DELTA.5-steroid-3 .beta.-ol dehydrogenase activity in testes was lowered by 24 %. With combined administration of estrogen and **antiandrogen**, an additive suppressive effect was obsd. which was comparable with the effect of castration regarding the wts. of the ventral prostate anterior prostatic lobe and seminal vesicles. The content of fructose in the tissues of the anterior prostatic lobe dropped abruptly. Total DNA content and the no. of cells in the ventral prostate decreased by 56 % to the postcastration level, though sep. administration of drugs caused no significant changes of these parameters. It is concluded that the antiprostatic effect of low doses of hexestrol in combination with flutamide is provided by antigonadotropic and antiandrogenic effects. This combination is supposed to be reasonable in the treatment of **prostatic cancer**.

ST **antiandrogen** estrogen pituitary testis prostate; **prostatic cancer antiandrogen** estrogen antitumor; hexestrol flutamide pituitary testis prostate

IT 9002-67-9, **LH**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(antiandrogen and low dose estrogen effect on pituitary-gonadal axis and prostate)

IT 57-48-7, Fructose, biological studies 58-22-0, **Testosterone** 9044-85-3
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(antiandrogen and low dose estrogen effect on pituitary-gonadal axis and prostate)

L10 ANSWER 9 OF 30 CAPLUS COPYRIGHT 2001 ACS

AB TZP 4238 is a new potent, orally active steroidal **antiandrogen**. Antiandrogenic activity and endocrinol. profile of TZP 4238 were investigated in rats, except that progestational activity was detd. in rabbits. TZP 4238 suppressed the **testosterone** propionate-induced increases in the wts. of the ventral prostate, seminal vesicle and levator ani in castrated immature male rats. TZP 4238 also decreased the wts. of the ventral prostate, seminal vesicle and levator ani in intact adult male rats, but did not affect the wt. of the testis or the serum concns. of **LH** and **testosterone**. TZP 4238 did not have such an inhibitory effect on the wt. of the adrenal gland as seen in other steroidal antiandrogens. It exhibited potent progestational activity. Although TZP 4238 did not exert androgenic or estrogenic activity, it had weak antiestrogenic activity. These results suggest that TZP 4238 exerts an antiandrogenic effect on the prostate without any compensatory change in the serum concn. of **LH** or **testosterone** in rats, and it is a useful drug for the treatment of androgen-dependent diseases such as **prostatic** hypertrophy and **prostatic cancer**.

ACCESSION NUMBER: 1995:523780 CAPLUS
DOCUMENT NUMBER: 122:282491
TITLE: Antiandrogenic activity and endocrinological profile of a novel antiandrogen, TZP-4238, in the rat
AUTHOR(S): Mieda, Mamoru; Ohta, Yoshihiro; Saito, Tomoyuki; Takahashi, Hiroo; Shimazawa, Eiichiro; Miyasaka, Katsuhiko
CORPORATE SOURCE: Pharmacological Research Department, Teikoku Hormone Mfg. Co., Ltd., Kawasaki, 213, Japan
SOURCE: Endocr. J. (Tokyo) (**1994**), 41(4), 445-52
CODEN: ENJOEO; ISSN: 0918-8959
DOCUMENT TYPE: Journal
LANGUAGE: English

SO Endocr. J. (Tokyo) (**1994**), 41(4), 445-52
CODEN: ENJOEO; ISSN: 0918-8959
AB TZP 4238 is a new potent, orally active steroidal **antiandrogen**. Antiandrogenic activity and endocrinol. profile of TZP 4238 were investigated in rats, except that progestational activity was detd. in rabbits. TZP 4238 suppressed the **testosterone** propionate-induced increases in the wts. of the ventral prostate, seminal vesicle and levator ani in castrated immature male rats. TZP 4238 also decreased the wts. of the ventral prostate, seminal vesicle and levator ani in intact adult male rats, but did not affect the wt. of the testis or the serum concns. of **LH** and **testosterone**. TZP 4238 did not have such an inhibitory effect on the wt. of the adrenal gland as seen in other steroidal antiandrogens. It exhibited potent progestational activity. Although TZP 4238 did not exert androgenic or estrogenic activity, it had weak antiestrogenic activity. These results suggest that TZP 4238 exerts an antiandrogenic effect on the prostate without any compensatory change in the serum concn. of **LH** or **testosterone** in rats, and it is a useful drug for the treatment of androgen-dependent diseases such as **prostatic** hypertrophy and **prostatic cancer**.

IT 57-85-2, **Testosterone** propionate
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(antiandrogenic activity and endocrinol. profile of TZP 4238)

L10 ANSWER 10 OF 30 CAPLUS COPYRIGHT 2001 ACS
AB Casodex (Zeneca) is a new potent, long-acting non-steroidal **anti**

-**androgen**, which produces androgen deprivation by blocking the androgen receptor. The authors evaluated the endocrine effects of Casodex 150 mg daily given in monotherapy as primary treatment for patients with **prostate cancer**. As part of a large, multicenter study comparing the therapeutic effects of surgical castration with 150 mg/day Casodex in monotherapy for patients with **prostate cancer**, a subgroup of 23 patients on Casodex were studied in detail for changes in endocrine parameters. Serum levels of **LH**, FSH, **testosterone**, dihydrotestosterone (DHT), estradiol, prolactin, sex hormone binding globulin and free **testosterone** were measured at the start of therapy and after 1, 4, 8, 12 and 24 wk. Effects on libido, sexual activity and the appearance of hot flushes, breast pain and gynecomastia were recorded. Administration of Casodex resulted in a rise in **LH** levels in all patients with a mean increase after 24 wk of 102%. Mean FSH levels showed a limited increase (7%) after 24 wk, which was significant only after 1 wk. As a result of the high **LH** levels, total **testosterone** levels increased after 24 wk by 66%, free **testosterone** by 57% and dihydrotestosterone by 24%. Parallel to **testosterone**, estradiol levels rose by a mean of 66%. Mean sex hormone binding globulin and prolactin levels rose by resp. 8% and 65%. Despite an increase in **testosterone** levels, excellent androgen blockade was obtained, as shown by a decrease in prostate specific antigen levels in 22/23 patients. Libido was maintained in 8/11 patients, and sexual activity in 5/6. No patient complained of hot flushes. However, mild gynecomastia and/or breast tenderness were seen in 48 and 30% of cases, resp. Thus, Casodex 150 mg/day monotherapy resembles surgical castration in achieving androgen deprivation, despite an increase in **LH** and **testosterone** levels. In contrast to castration, libido and sexual activity are usually maintained and hot flushes are rare. However, mild gynecomastia and/or breast tenderness were noted in 48 and 30% of patients.

ACCESSION NUMBER: 1995:197748 CAPLUS
DOCUMENT NUMBER: 122:632
TITLE: Endocrine profiles during administration of the new non-steroidal **anti-androgen** Casodex in **prostate cancer**
AUTHOR(S): Verhelst, J.; Denis, L.; Van Vliet, P.; Van Poppel, H.; Braeckman, J.; Van Cangh, P.; Mattelaer, J.; D'Hulster, D.; Mahler, C.
CORPORATE SOURCE: Department of Endocrinology, St Elisabeth Hospital, Antwerp, Belg.
SOURCE: Clin. Endocrinol. (Oxford) (**1994**), 41(4), 525-30
CODEN: CLECAP; ISSN: 0300-0664
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Endocrine profiles during administration of the new non-steroidal **anti-androgen** Casodex in **prostate cancer**
SO Clin. Endocrinol. (Oxford) (**1994**), 41(4), 525-30
CODEN: CLECAP; ISSN: 0300-0664
AB Casodex (Zeneca) is a new potent, long-acting non-steroidal **anti-androgen**, which produces androgen deprivation by blocking the androgen receptor. The authors evaluated the endocrine effects of Casodex 150 mg daily given in monotherapy as primary treatment for patients with **prostate cancer**. As part of a large, multicenter study comparing the therapeutic effects of surgical castration with 150 mg/day Casodex in monotherapy for patients with **prostate cancer**

, a subgroup of 23 patients on Casodex were studied in detail for changes in endocrine parameters. Serum levels of **LH**, FSH, **testosterone**, dihydrotestosterone (DHT), estradiol, prolactin, sex hormone binding globulin and free **testosterone** were measured at the start of therapy and after 1, 4, 8, 12 and 24 wk. Effects on libido, sexual activity and the appearance of hot flushes, breast pain and gynecomastia were recorded. Administration of Casodex resulted in a rise in **LH** levels in all patients with a mean increase after 24 wk of 102%. Mean FSH levels showed a limited increase (7%) after 24 wk, which was significant only after 1 wk. As a result of the high **LH** levels, total **testosterone** levels increased after 24 wk by 66%, free **testosterone** by 57% and dihydrotestosterone by 24%. Parallel to **testosterone**, estradiol levels rose by a mean of 66%. Mean sex hormone binding globulin and prolactin levels rose by resp. 8% and 65%. Despite an increase in **testosterone** levels, excellent androgen blockade was obtained, as shown by a decrease in prostate specific antigen levels in 22/23 patients. Libido was maintained in 8/11 patients, and sexual activity in 5/6. No patient complained of hot flushes. However, mild gynecomastia and/or breast tenderness were seen in 48 and 30% of cases, resp. Thus, Casodex 150 mg/day monotherapy resembles surgical castration in achieving androgen deprivation, despite an increase in **LH** and **testosterone** levels. In contrast to castration, libido and sexual activity are usually maintained and hot flushes are rare. However, mild gynecomastia and/or breast tenderness were noted in 48 and 30% of patients.

ST **antiandrogen** Casodex endocrine system **prostate cancer**

IT Endocrine system
Gynecomastia
Sexual behavior
(endocrine profiles during administration of new non-steroidal **anti-androgen** Casodex in **prostate cancer** in humans)

IT Globulins, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(SHBG (sex hormone-binding globulin), endocrine profiles during administration of new non-steroidal **anti-androgen** Casodex in **prostate cancer** in humans)

IT Androgens
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiandrogens, endocrine profiles during administration of new non-steroidal **anti-androgen** Casodex in **prostate cancer** in humans)

IT Prostate gland
(neoplasm, inhibitors, endocrine profiles during administration of new non-steroidal **anti-androgen** Casodex in **prostate cancer** in humans)

IT Neoplasm inhibitors
(prostate gland, endocrine profiles during administration of new non-steroidal **anti-androgen** Casodex in **prostate cancer** in humans)

IT 90357-06-5, Casodex
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endocrine profiles during administration of new non-steroidal **anti-androgen** Casodex in **prostate cancer** in humans)

IT 50-28-2, Estradiol, biological studies 58-22-0, **Testosterone**
521-18-6, Dihydrotestosterone 9002-62-4, Prolactin, biological studies
9002-67-9, **LH** 9002-68-0, FSH
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(endocrine profiles during administration of new non-steroidal **anti-androgen** Casodex in **prostate cancer** in humans)

L10 ANSWER 11 OF 30 CAPLUS COPYRIGHT 2001 ACS
AB Administration of antiprogesterone RU 486 to female cyclic rats results in blockade of ovulation assocd. with both a decreased ovulatory release of **LH** and an increased rate of follicular **atresia**. These rats also exhibit increased **LH**:FSH and **testosterone**:estradiol ratios in serum during the period of follicular development as well as an increase in serum concns. of prolactin that can be suppressed by a dopamine agonist. The increase in either prolactin or **testosterone** concns. as well as the relative deficiency in FSH might be responsible for the increase in follicular **atresia**. The present work evaluated the involvement of **LH**, FSH, prolactin and **testosterone** in follicular **atresia** and in blockade of ovulation induced by RU 486 in the cyclic rat. Although bromocriptine treatment did not modify the blockade of ovulation induced by RU 486, unilateral ovariectomy at metestrus and **antiandrogen** flutamide treatment reversed, in part, the effects of RU 486 on both follicular development and ovulation. The combined increase in FSH serum concn. during diestrus induced by unilateral ovariectomy and the treatment with flutamide had no additive effects. Furthermore, treatment with a superovulatory amt. of hFSH did not reverse the effects of RU 486. Moreover, unilateral ovariectomy halved **testosterone** serum concns. and flutamide treatment had no effect on **LH** and FSH concns. in RU 486-treated rats. It was therefore concluded that androgens play a role, at least in part, in the process of follicular **atresia** induced by RU 486.

ACCESSION NUMBER: 1994:23756 CAPLUS
DOCUMENT NUMBER: 120:23756
TITLE: Evidence that androgens are involved in atresia and anovulation induced by antiprogesterone RU486 in rats
AUTHOR(S): Sanchez-Criado, J. E.; Tebar, M.; Sanchez, A.; Gaytan, F.
CORPORATE SOURCE: Fac. Med., Univ. Cordoba, Cordoba, 14004, Spain
SOURCE: J. Reprod. Fertil. (**1993**), 99(1), 173-9
CODEN: JRPFA4; ISSN: 0022-4251
DOCUMENT TYPE: Journal
LANGUAGE: English
SO J. Reprod. Fertil. (**1993**), 99(1), 173-9
CODEN: JRPFA4; ISSN: 0022-4251
AB Administration of antiprogesterone RU 486 to female cyclic rats results in blockade of ovulation assocd. with both a decreased ovulatory release of **LH** and an increased rate of follicular **atresia**. These rats also exhibit increased **LH**:FSH and **testosterone**:estradiol ratios in serum during the period of follicular development as well as an increase in serum concns. of prolactin that can be suppressed by a dopamine agonist. The increase in either prolactin or **testosterone** concns. as well as the relative deficiency in FSH might be responsible for the increase in follicular **atresia**. The present work evaluated the involvement of **LH**, FSH, prolactin and **testosterone** in follicular **atresia** and in blockade of ovulation induced by RU 486 in the cyclic rat. Although bromocriptine

treatment did not modify the blockade of ovulation induced by RU 486, unilateral ovariectomy at metestrus and **antiandrogen** flutamide treatment reversed, in part, the effects of RU 486 on both follicular development and ovulation. The combined increase in FSH serum concn. during diestrus induced by unilateral ovariectomy and the treatment with flutamide had no additive effects. Furthermore, treatment with a superovulatory amt. of hFSH did not reverse the effects of RU 486. Moreover, unilateral ovariectomy halved **testosterone** serum concns. and flutamide treatment had no effect on **LH** and FSH concns. in RU 486-treated rats. It was therefore concluded that androgens play a role, at least in part, in the process of follicular **atresia** induced by RU 486.

IT 9002-62-4, Prolactin, biological studies 9002-67-9, **LH** 9002-68-0, FSH
RL: BIOL (Biological study)
(ovary follicle atresia and anovulation induction by RU 486 in relation to)

IT 58-22-0, **Testosterone**
RL: BIOL (Biological study)
(ovary follicle atresia and anovulation induction by RU 486 regulation by)

L10 ANSWER 12 OF 30 CAPLUS COPYRIGHT 2001 ACS

AB The claimed ability of non-steroidal antiandrogens to preserve libido and sexual potency is sought as a potential improvement in the palliative management of **prostate cancer**. A crit. issue for the clin. use of these compds. is, however, the reported evidence in the rat of an excessive increase in **testosterone** concns. as a consequence of the androgen neg. feedback interruption. On the other hand, the recovery of testicular function after long-term inhibition by **LH**-RH analogs is also an important concern in view of the proposed use of these compds. for the treatment of several non-malignant conditions. The authors addressed these issues by studying the long-term endocrine effects induced by the administration of either the non-steroidal **antiandrogen** nilutamide or the depot prepn. of D-Trp6-LHRH in men with **prostate cancer**. Treatment with the **antiandrogen** induced a marked increase in gonadotropin levels, **LH** concns. rising from a mean of 17.5 to a max. of 56.6 kU/L, while mean **testosterone** and 17.beta. estradiol- concns. rose only by about 50 and 70% over pretreatment values, **testosterone** levels reaching a plateau after 1 mo of treatment. In the subjects treated with the LHRH agonist, 6 mo after discontinuation of long-term administration, the mean **LH** had risen to 36.9 IU/L while mean **testosterone** levels were still as low as 1.7 and rose only to a max. of 4.2 nmol/L after high-dose human chorionic gonadotropin loadings. The authors conclude that in elderly men with **prostate cancer**: stimulation of the entire axis by non-steroidal antiandrogens induces only a mild **testosterone** increase, the testis being the site of the reduced response and prolonged inhibition of the pituitary-gonadal axis induced by LHRH agonists may not be reversible at the testicular level.

ACCESSION NUMBER: 1994:846 CAPLUS
DOCUMENT NUMBER: 120:846
TITLE: Long-term endocrine effects of administration of either a non-steroidal **antiandrogen** or a **luteinizing hormone**-releasing **hormone** agonist in men with **prostate cancer**

09/889,904

AUTHOR(S): Decensi, Andrea; Torrisi, Rosalba; Fontana, Vincenzo; Marroni, Paola; Guarneri, Domenico; Minuto, Francesco; Boccardo, Francesco

CORPORATE SOURCE: Dep. Med. Oncol. II, Natl. Inst. Cancer Res., Genoa, 16132, Italy

SOURCE: Acta Endocrinol. (**1993**), 129(4), 315-21
CODEN: ACENA7; ISSN: 0001-5598

DOCUMENT TYPE: Journal

LANGUAGE: English

TI Long-term endocrine effects of administration of either a non-steroidal **antiandrogen** or a **luteinizing hormone** -releasing **hormone** agonist in men with **prostate cancer**

SO Acta Endocrinol. (**1993**), 129(4), 315-21
CODEN: ACENA7; ISSN: 0001-5598

AB The claimed ability of non-steroidal antiandrogens to preserve libido and sexual potency is sought as a potential improvement in the palliative management of **prostate cancer**. A crit. issue for the clin. use of these compds. is, however, the reported evidence in the rat of an excessive increase in **testosterone** concns. as a consequence of the androgen neg. feedback interruption. On the other hand, the recovery of testicular function after long-term inhibition by **LH**-RH analogs is also an important concern in view of the proposed use of these compds. for the treatment of several non-malignant conditions. The authors addressed these issues by studying the long-term endocrine effects induced by the administration of either the non-steroidal **antiandrogen** nilutamide or the depot prepn. of D-Trp6-LHRH in men with **prostate cancer**. Treatment with the **antiandrogen** induced a marked increase in gonadotropin levels, **LH** concns. rising from a mean of 17.5 to a max. of 56.6 kU/L, while mean **testosterone** and 17.beta. estradiol- concns. rose only by about 50 and 70% over pretreatment values, **testosterone** levels reaching a plateau after 1 mo of treatment. In the subjects treated with the LHRH agonist, 6 mo after discontinuation of long-term administration, the mean **LH** had risen to 36.9 IU/L while mean **testosterone** levels were still as low as 1.7 and rose only to a max. of 4.2 nmol/L after high-dose human chorionic gonadotropin loadings. The authors conclude that in elderly men with **prostate cancer**: stimulation of the entire axis by non-steroidal antiandrogens induces only a mild **testosterone** increase, the testis being the site of the reduced response and prolonged inhibition of the pituitary-gonadal axis induced by LHRH agonists may not be reversible at the testicular level.

IT Blood
(gonadotropins and steroids of, after androgen inhibitor or **LH** -RH agonist treatment in prostate cancer in men)

IT Endocrine system
(anterior pituitary-testis, androgen inhibitor or **LH**-RH agonist effect on, in prostate cancer in men)

IT Prostate gland
(neoplasm, gonadotropin and steroid secretion response to antiandrogen and **LH**-RH agonist in, in men)

IT 50-28-2, Estradiol, biological studies 58-22-0, **Testosterone** 9002-62-4, PRL, biological studies 9002-67-9, **LH** 9002-68-0, FSH
RL: BIOL (Biological study)
(secretion of, androgen inhibitor and **LH**-RH agonist effect on, in prostate cancer in men)

L10 ANSWER 13 OF 30 CAPLUS COPYRIGHT 2001 ACS
AB Administration of antiprogestagens mifepristone (RU486) and onapristone (ZK299) to female cyclic rats resulted in blockade of ovulation. However, the antiprogestagens did not block the ovulatory process in the cyclic hamster, probably because RU486 and ZK299 have no affinity to the hamster progesterone receptor. Antiprogestagen-treated rats exhibited increased **LH** concns. during the period of follicular development and an increased **testosterone**/estradiol ratio. **Antiandrogen** flutamide treatment or an ovulatory injection of hCG reversed, in part, the **anovulatory** action of RU486. When flutamide treatment was combined with hCG injection, no full ovulation rate was obtained in RU486-treated rats. Thus, besides androgens, other factors assocd. with the action of progesterone at the follicular level may be involved in RU486-induced **atresia** and ovulatory blockade. A redn. in the amt. of ovulatory **LH** released was also responsible for the ovulatory deficit in RU486-treated rats.
ACCESSION NUMBER: 1993:509226 CAPLUS
DOCUMENT NUMBER: 119:109226
TITLE: Progesterone antagonists (mifepristone and onapristone) and ovulation in rats and hamsters
AUTHOR(S): Sanchez-Criado, J. E.; Uilenbroek, J. T. J.
CORPORATE SOURCE: Fac. Med., Univ. Cordoba, Cordoba, 14004, Spain
SOURCE: Adv. Contracept. Delivery Syst. (**1993**), 9(2-3), 151-63
CODEN: ACDSEL; ISSN: 1012-8689
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Adv. Contracept. Delivery Syst. (**1993**), 9(2-3), 151-63
CODEN: ACDSEL; ISSN: 1012-8689
AB Administration of antiprogestagens mifepristone (RU486) and onapristone (ZK299) to female cyclic rats resulted in blockade of ovulation. However, the antiprogestagens did not block the ovulatory process in the cyclic hamster, probably because RU486 and ZK299 have no affinity to the hamster progesterone receptor. Antiprogestagen-treated rats exhibited increased **LH** concns. during the period of follicular development and an increased **testosterone**/estradiol ratio. **Antiandrogen** flutamide treatment or an ovulatory injection of hCG reversed, in part, the **anovulatory** action of RU486. When flutamide treatment was combined with hCG injection, no full ovulation rate was obtained in RU486-treated rats. Thus, besides androgens, other factors assocd. with the action of progesterone at the follicular level may be involved in RU486-induced **atresia** and ovulatory blockade. A redn. in the amt. of ovulatory **LH** released was also responsible for the ovulatory deficit in RU486-treated rats.

L10 ANSWER 14 OF 30 CAPLUS COPYRIGHT 2001 ACS
AB Administration of the antiprogesterone RU 486 (4 mg/day) from estrus through proestrus to cyclic rats blocked ovulation. Moreover, RU 486 increased basal serum concns. of **LH**, PRL, **testosterone** and estradiol, while it decreased the basal serum concn. of FSH. Both unilateral ovariectomy and **antiandrogen** flutamide treatment, as well as an ovulatory injection of human chorionic gonadotropin (HCG) in the proestrus afternoon partially reversed, the ovulatory blockade of RU 486. Apparently, both the decreased FSH concn. and the increased **testosterone** concn., as well as the reduced ovulatory **LH** release are responsible for the **anovulatory** effects of RU 486.
ACCESSION NUMBER: 1993:486461 CAPLUS

DOCUMENT NUMBER: 119:86461
TITLE: Unilateral ovariectomy, flutamide treatment and HCG reverse the anovulatory action of antiprogesterone RU486 in rat
AUTHOR(S): Tebar, M.; Sanchez, A.; Sanchez-Criado, J. E.
CORPORATE SOURCE: Fac. Med., Univ. Cordoba, Cordoba, 14004, Spain
SOURCE: Rev. Esp. Fisiol. (**1992**), 48(4), 259-64
CODEN: REFIAS; ISSN: 0034-9402
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Rev. Esp. Fisiol. (**1992**), 48(4), 259-64
CODEN: REFIAS; ISSN: 0034-9402
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IT Ovulation
(inhibition of, by RU 486, gonadotropin and **testosterone** role in)
IT Progestogens
RL: BIOL (Biological study)
(inhibitors, RU 486 as, ovulation inhibition by, gonadotropin and **testosterone** role in)
IT 50-28-2, Estradiol, biological studies 58-22-0, **Testosterone**
9002-62-4, Prolactin, biological studies 9002-67-9, **LH**
9002-68-0, FSH
RL: BIOL (Biological study)
(ovulation inhibition by RU 486 in relation to)
IT 84371-65-3, RU486
RL: BIOL (Biological study)
(ovulation inhibition by, gonadotropin and **testosterone** role in)

L10 ANSWER 15 OF 30 CAPLUS COPYRIGHT 2001 ACS
AB In order to mimic the human situation in which adrenal steroid precursors are converted to the active androgen dihydrotestosterone (DHT) in prostatic tissue, castrated rats supplemented with the precursor steroid androstenedione (.DELTA.4-dione) released from Silastic implants, were used. While it is well known that the action of DHT can be partially neutralized by antiandrogens which compete for binding to the androgen receptor, 17.beta.-N,N-diethylcarbamoyl-4-methyl-4-aza-5.alpha.-androstan-3-one (4-MA), an inhibitor of 5.alpha.-reductase, the enzyme which converts **testosterone** into DHT, was used, in order to decrease intraprostatic DHT levels and thus facilitate the action of the antiandrogen. Animals were treated for 7 days with Flutamide (FLU, 2 mg) or 4-MA (4 mg) injected s.c., twice daily, alone or in combination. 4-MA administered alone caused a 54% inhibition of .DELTA.4-dione-stimulated ventral prostate wt. while FLU exerted a 74% inhibitory effect and 4-MA + FLU further improved inhibition to 81%. The levels of prostatic mRNAs encoding the C1 and C3 components of the prostatic binding protein (PBP) which are highly specific and sensitive markers of androgen action, were then measured by in situ hybridization. PBP-C3 mRNA levels fell by 95%

following castration while treatment with .DELTA.4-dione completely reversed the effect of castration. Administration of FLU or 4-MA independently caused 33% and 10% decreases, resp., of PBP-C3 mRNA levels stimulated by .DELTA.4-dione while the combination of both compds. further inhibited PBP-C3 mRNA levels to reach a 55% inhibition. Similar effects were obsd. on PBP-C1 mRNA levels. Moreover, while FLU or 4-MA alone caused 72 and 75% decreases in intraprostatic DHT levels, resp., the combined treatment caused a 89% decrease in the intraprostatic concn. of the androgen. The present data show that the combination of a pure antiandrogen and a 5.alpha.-reductase inhibitor has greater inhibitory effects than either compd. used alone on androgen-sensitive parameters in the rat ventral prostate. It is likely that an important part of the beneficial effect of the antiandrogen is due to its blockade of access to the androgen receptor of the high intraprostatic levels of **testosterone** resulting from the action of the 5.alpha.-reductase inhibitor used alone.

ACCESSION NUMBER: 1993:205457 CAPLUS
DOCUMENT NUMBER: 118:205457
TITLE: Blockade of androstenedione-induced stimulation of androgen-sensitive parameters in the rat prostate by combination of Flutamide and 4-MA
AUTHOR(S): Martel, Celine; Trudel, Claude; Couet, Jacques; Labrie, Claude; Belanger, Alain; Labrie, Fernand
CORPORATE SOURCE: MRC Group Mol. Endocrinol., CHUL Res. Cent., Quebec, PQ, G1V 4G2, Can.
SOURCE: Mol. Cell. Endocrinol. (**1993**), 91(1-2), 43-9
CODEN: MCEND6; ISSN: 0303-7207
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Mol. Cell. Endocrinol. (**1993**), 91(1-2), 43-9
CODEN: MCEND6; ISSN: 0303-7207
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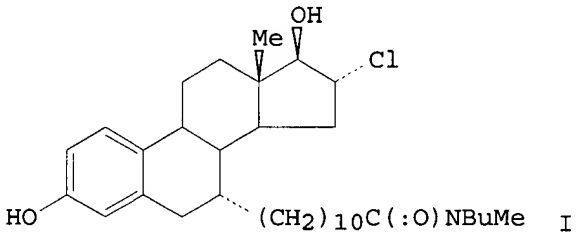
ST flutamide diethylcarbamoylmethylazaandrostanone androstenedione androgen prostate; **antiandrogen** steroid reductase inhibitor prostate androgen; **prostate cancer antiandrogen** steroid reductase inhibitor

IT 58-22-0, **Testosterone**
RL: BIOL (Biological study)
(of blood serum, androstenedione increase of, antiandrogen and steroid reductase inhibitor enhancement of)

IT 9002-67-9, **LH** 9002-68-0, FSH
RL: BIOL (Biological study)
(of blood serum, androstenedione inhibition of, antiandrogen and steroid reductase inhibitors inhibition of)

L10 ANSWER 16 OF 30 CAPLUS COPYRIGHT 2001 ACS
GI



I

AB A method of treatment of androgen-related diseases (e.g. prostate cancer) in male humans or warm-blooded animals comprises administering novel antiandrogens and/or novel sex steroid biosynthesis inhibitors as part of a combination therapy. Sex steroid biosynthesis inhibitors, esp. those capable of inhibiting conversion of dehydroepiandrosterone or 4-androstenedione to natural sex steroids (and **testosterone** into dihydrotestosterone) in peripheral tissues, are used in combination with antiandrogens usually after blockade of testicular hormonal secretions. Antiestrogens can also be part of the combination therapy. Pharmaceutical compns. and 2-, 3-, 4-, and 5-component kits are useful for such combination treatment. EM139 (I) was prepd. starting from 19-nortestosterone by protection, addn. to undecanol by Grignard reaction, dehydrogenation and deprotection, oxidn. and amidation with BuNHMe, acetylenolation, and chlorination.

ACCESSION NUMBER: 1991:485452 CAPLUS
DOCUMENT NUMBER: 115:85452
TITLE: Preparation of steroidal enzyme inhibitors for treatment of prostate cancer
INVENTOR(S): Labrie, Fernand
PATENT ASSIGNEE(S): Endorecherche Inc., Can.
SOURCE: PCT Int. Appl., 102 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 9100733	A1	19910124	WO 1990-CA212	19900705	<--
W: AT, AU, BB, BG, BR, CA, CH, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MW, NL, NO, RO, SD, SE, SU					
RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE					
CA 2062792	AA	19910108	CA 1990-2062792	19900705	<--
AU 9058516	A1	19910206	AU 1990-58516	19900705	<--
HU 60139	A2	19920828	HU 1992-48	19900705	<--
JP 04506799	T2	19921126	JP 1990-509263	19900705	<--
EP 595796	A1	19940511	EP 1990-909601	19900705	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE					
ZA 9005313	A	19920226	ZA 1990-5313	19900706	<--
IL 94991	A1	19991130	IL 1990-94991	19900706	
US 5372996	A	19941213	US 1992-963278	19921019	<--
US 5593981	A	19970114	US 1993-98607	19930910	<--
AU 9463425	A1	19940721	AU 1994-63425	19940530	<--
AU 665311	B2	19951221			
US 5610150	A	19970311	US 1995-472512	19950607	<--

PRIORITY APPLN. INFO.:

US 1989-376710	A	19890707	
US 1989-322154	B2	19890310	
WO 1990-CA212	A	19900705	
US 1992-963278	A3	19921019	
US 1993-98607	A3	19930910	

OTHER SOURCE(S): MARPAT 115:85452
PI WO 9100733 A1 **19910124**

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI WO 9100733	A1	19910124	WO 1990-CA212	19900705	<--
W: AT, AU, BB, BG, BR, CA, CH, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MW, NL, NO, RO, SD, SE, SU					
RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE					
CA 2062792	AA	19910108	CA 1990-2062792	19900705	<--
AU 9058516	A1	19910206	AU 1990-58516	19900705	<--
HU 60139	A2	19920828	HU 1992-48	19900705	<--
JP 04506799	T2	19921126	JP 1990-509263	19900705	<--
EP 595796	A1	19940511	EP 1990-909601	19900705	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE					
ZA 9005313	A	19920226	ZA 1990-5313	19900706	<--
IL 94991	A1	19991130	IL 1990-94991	19900706	
US 5372996	A	19941213	US 1992-963278	19921019	<--
US 5593981	A	19970114	US 1993-98607	19930910	<--
AU 9463425	A1	19940721	AU 1994-63425	19940530	<--
AU 665311	B2	19951221			
US 5610150	A	19970311	US 1995-472512	19950607	<--

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ST **prostate cancer antiandrogen** male steroid

IT 9034-40-6, **Luteinizing hormone**-releasing factor
RL: BIOL (Biological study)
(agonists and antagonists, for prostate cancer treatment)

L10 ANSWER 17 OF 30 CAPLUS COPYRIGHT 2001 ACS

AB To assess the biol. significance of low serum androgens comparable to those which remain after castration in men treated for **prostate cancer**, Silastic depots continuously releasing predetd. doses of **testosterone** (T) were implanted into castrated adult male rats in the absence or presence of simultaneous treatment with the pure **antiandrogen** Flutamide. A 3-5-fold increase in prostate wt. was obsd. at plasma T concns. comparable to those found in the serum of castrate men. Although of lower magnitude, castration levels of plasma T also stimulated seminal vesicle wt. This dramatic stimulatory influence of castration levels of plasma T on ventral prostate and seminal vesicle wt. can be explained by the 13-15-fold higher intraprostatic level of the active androgen dihydrotestosterone (DHT) compared to the plasma T concn. In fact, a near-maximal intraprostatic concn. of DHT is reached at concns. of plasma T of 0.2-0.5 ng/mL and a pos. correlation was found between prostatic DHT concn. and ventral prostate wt. Prostatic growth and DHT concns. were also pos. correlated with ornithine decarboxylase (ODC) activity, an enzyme highly sensitive to androgens in the rat ventral prostate. A dramatic (30-fold) increase in ODC activity was obsd. at plasma T values corresponding to those found in castrated men. The level of prostatic .beta.2-adrenergic receptors fell within 10 days of castration and an increase in .beta.2-adrenergic receptor concn. was obsd. with low doses of T, thus indicating that .beta.2-adrenoreceptor levels are also a sensitive parameter of androgenic activity in the rat prostate. Concomitant treatment with Flutamide, while having no effect by itself, completely prevented the stimulatory effect of T on prostate wt., ODC activity, and .beta.2-adrenergic receptor levels in the rat prostate. Evidently, plasma T levels in the range found in castrated men (0.2-0.5 ng/mL) have major androgenic activity in the rat prostate. Apparently, in addn. to the blockade (by treatment with **LH**-RH agonist) or removal (by orchiectomy) of testicular androgens, an improved therapy of prostatic carcinoma requires simultaneously blockade of the so-far neglected but biol. important androgens of adrenal origin which, otherwise, are left free to stimulate **prostatic cancer** after castration.

ACCESSION NUMBER: 1989:18649 CAPLUS
DOCUMENT NUMBER: 110:18649
TITLE: Castration levels of plasma **testosterone** have potent stimulatory effects on androgen-sensitive parameters in the rat prostate
AUTHOR(S): Marchetti, B.; Poulin, R.; Plante, M.; Labrie, Fernand
CORPORATE SOURCE: Le Cent. Hosp., Univ. Laval, Quebec, PQ, G1V 4G2, Can.
SOURCE: J. Steroid Biochem. (**1988**), 31(4A), 411-19
CODEN: JSTBBK; ISSN: 0022-4731
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Castration levels of plasma **testosterone** have potent stimulatory effects on androgen-sensitive parameters in the rat prostate

SO J. Steroid Biochem. (**1988**), 31(4A), 411-19
CODEN: JSTBBK; ISSN: 0022-4731

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ST **testosterone** plasma castration biol activity; prostate androgen sensitivity castration

IT Castration
(**testosterone** of blood plasma in, prostate gland response to)

IT Blood plasma
(**testosterone** of, after castration, prostate gland response to)

IT 58-22-0, **Testosterone**
RL: BIOL (Biological study)
(of blood plasma, after castration, prostate gland response to)

L10 ANSWER 18 OF 30 CAPLUS COPYRIGHT 2001 ACS

AB Daily s.c. administration of 50 .mu.g of the **LH**-RH agonist [D-Trp6]**LH**-RH ethylamide in adult dogs causes a transient increase in the serum **testosterone** (T) concn. which reaches a max. at 200% above control on days 2-4 of treatment and progressively decreases to 7% of the pretreatment value on day 21, the last time interval studied. After a transient increase, the concn. of serum bioactive **LH** was progressively decreased on days 11 and 19, thus suggesting that in analogy with human findings, the loss of **LH** bioactivity is responsible for the inhibition of testicular steroidogenesis induced in the dog by **LH**-RH agonists. Of major

significance is the finding that the changes in serum T levels obsd. during the 1st 3 wk of treatment, as well as the complete inhibition of the intratesticular concn. of sex steroids obsd. at the end of this period of treatment with the **LH**-RH agonist were not affected by simultaneous administration of flutamide (125 mg per os every 8 h). Such findings indicate that at the dose used, the **LH**-RH agonist is in full control of gonadotropin secretion, thus completely overcoming feedback influences. Since the administration of the **antiandrogen** flutamide does not decrease the efficacy of the **LH**-RH agonist as blocker of testicular androgen biosynthesis, the present data support the use of a pure **antiandrogen** to neutralize the effect of the transient rise in testicular androgen secretion which always accompanies the 1st days of treatment with **LH**-RH agonists in patients with advanced **prostate cancer**.

ACCESSION NUMBER: 1988:180332 CAPLUS
DOCUMENT NUMBER: 108:180332
TITLE: A pure antiandrogen does not interfere with the **LH**-RH agonist-induced blockade of testicular androgen secretion in the dog
AUTHOR(S): Lacoste, D.; St-Arnaud, R.; Belanger, A.; Labrie, F.
CORPORATE SOURCE: Med. Cent., Laval Univ., Quebec, PQ, G1V 4G2, Can.
SOURCE: Mol. Cell. Endocrinol. (**1988**), 56(1-2), 141-7
CODEN: MCEND6; ISSN: 0303-7207
DOCUMENT TYPE: Journal
LANGUAGE: English

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CODEN: MCEND6; ISSN: 0303-7207

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IT Testis, metabolism
(androgen secretion by, **LH**-RH analog inhibition of, flutamide effect on)

IT Androgens

RL: BIOL (Biological study)
(secretion of, by testis, **LH**-RH agonist inhibition of, flutamide effect on)

IT Blood serum
(**testosterone** of, **LH**-RH agonist effect on, flutamide in relation to)

IT 13311-84-7, Flutamide
RL: BIOL (Biological study)
(androgen secretion by testis inhibition by **LH**-RH agonist in relation to)

IT 50-28-2, Estradiol, biological studies 53-43-0 57-83-0, Progesterone, biological studies 63-05-8, Androstenedione 68-96-2, 17-Hydroxyprogesterone 145-13-1 387-79-1 521-17-5, Androst-5-en-3.beta.,17.beta.-diol 521-18-6, Dihydrotestosterone 1852-53-5, Androstane-3.alpha.,17.beta.-diol 33526-32-8, Androstane-3.beta.,17.beta.-diol
RL: BIOL (Biological study)
(of testis, flutamide and **LH**-RH agonist effect on)

IT 9002-67-9
RL: BIOL (Biological study)
(secretion of, **LH**-RH analog effect on, androgen release by testis in relation to)

IT 58-22-0, **Testosterone**
RL: BIOL (Biological study)
(secretion of, by testis, **LH**-RH agonist inhibition of, flutamide effect on)

L10 ANSWER 19 OF 30 CAPLUS COPYRIGHT 2001 ACS

AB An HPLC method is described for the measurement of the plasma levels of hydroxyflutamide (Flu-OH), the biol. active and main circulating metabolite of flutamide. Four h after oral administration of 250 mg flutamide to healthy young men, as well as to patients with **prostate cancer**, the plasma concn. of Flu-OH reached a peak at .apprx.1.7 .mu.M. The plasma concn. of Flu-OH measured at mon 6, 12, and 18 of treatment showed a minimal basal level of 3.4 .mu.M with a maximal increase at 6.8-8.5 .mu.M at 2-4 h. Since the serum levels of **testosterone** in these patients are .apprx.1 nM, the levels of the active **antiandrogen** are at a 5000-10,000-fold excess. However, due to the low affinity of the **antiandrogen** for the androgen receptor, it is extremely important to maintain this concn. of the **antiandrogen** in plasma const.

ACCESSION NUMBER: 1988:179557 CAPLUS
DOCUMENT NUMBER: 108:179557
TITLE: Plasma levels of hydroxyflutamide in patients with prostatic cancer receiving combined hormonal therapy: an **LH**-RH agonist and flutamide
AUTHOR(S): Belanger, Alain; Giasson, Marcelle; Couture, Jean; Dupont, Andre; Cusan, Leonello; Labrie, Fernand
CORPORATE SOURCE: Cent. Hosp., Univ. Laval, Quebec, PQ, G1V 4G2, Can.
SOURCE: Prostate (N. Y.) (**1988**), 12(1), 79-84
CODEN: PRSTDS; ISSN: 0270-4137
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Plasma levels of hydroxyflutamide in patients with prostatic cancer receiving combined hormonal therapy: an **LH**-RH agonist and flutamide

SO Prostate (N. Y.) (**1988**), 12(1), 79-84
CODEN: PRSTDS; ISSN: 0270-4137

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L10 ANSWER 20 OF 30 CAPLUS COPYRIGHT 2001 ACS

AB The effect of short term administration of flutamide on the hypothalamic-pituitary-gonadal axis was studied in patients with advanced **prostate cancer** (C2 stage). Flutamide increased **LH** pulse frequency in all patients. The FSH pulse anal. disclosed a similar pattern. Plasma intergrated concn. of **testosterone** (IC-T) clearly increased following flutamide therapy; mean IC-T values were 2.67 and 4.67 ng./mL before and after flutamide administration, resp. Thus, flutamide acts in humans as a selective and specific **antiandrogen**.

ACCESSION NUMBER: 1988:143698 CAPLUS
DOCUMENT NUMBER: 108:143698
TITLE: Short-term effects of flutamide administration on hypothalamic-pituitary-testicular axis in man
AUTHOR(S): Migliari, Roberto; Balzano, Stefano; Scarpa, Roberto Mario; Campus, Giuliana; Pintus, Cristina; Usai, Enzo
CORPORATE SOURCE: Dep. Urol., Univ. Cagliari, Cagliari, 09100, Italy
SOURCE: J. Urol. (Baltimore) (**1988**), 139(3), 637-9
CODEN: JOURAA; ISSN: 0022-5347
DOCUMENT TYPE: Journal
LANGUAGE: English

SO J. Urol. (Baltimore) (**1988**), 139(3), 637-9
CODEN: JOURAA; ISSN: 0022-5347

AB The effect of short term administration of flutamide on the hypothalamic-pituitary-gonadal axis was studied in patients with advanced **prostate cancer** (C2 stage). Flutamide increased **LH** pulse frequency in all patients. The FSH pulse anal. disclosed a similar pattern. Plasma intergrated concn. of **testosterone** (IC-T) clearly increased following flutamide therapy; mean IC-T values were 2.67 and 4.67 ng./mL before and after flutamide administration, resp. Thus, flutamide acts in humans as a selective and specific **antiandrogen**.

ST flutamide antiandrogen gonadotropin **testosterone** plasma

IT Blood plasma
(**testosterone** of, flutamide effect on, in men)

IT 13311-84-7, Flutamide
RL: BIOL (Biological study)
(gonadotropin and **testosterone** of blood plasma response to, in man, antiandrogenic activity in relation to)

IT 58-22-0, **Testosterone**
RL: BIOL (Biological study)
(of blood plasma, flutamide effect on, in men)

IT 9002-67-9, **LH** 9002-68-0, FSH
RL: BIOL (Biological study)

(pulsatile secretion of, flutamide effect on, in men)

L10 ANSWER 21 OF 30 CAPLUS COPYRIGHT 2001 ACS

AB Changes in plasma lipoproteins were studied in patients with **prostate cancer** during treatment with several androgen suppression therapies. Estrogen, orchiectomy, and a combination of **LH**-RH agonist and **antiandrogen** (flutamide) reduced plasma **testosterone** concns. (89-92%) and plasma estradiol decreased by 85, 44, and 54%, resp. Estrogen induced hypertriglyceridemia and elevation of plasma high-d. lipoprotein (HDL) cholesterol, phospholipid, and apolipoprotein A-I and A-II concns. Low-d. lipoprotein (LDL) cholesterol decreased but LDL apolipoprotein B did not. Apparently, the cardiovascular complications that occur during estrogen administration are not mediated through changes in lipoprotein profile, other than the hypertriglyceridemic effect. Orchiectomy caused hypercholesterolemia and an increase in both total and LDL apolipoprotein B, all of which are strong determinants of cardiovascular disease. The HDL concn. was not affected despite a redn. in plasma **testosterone**, perhaps due to a simultaneous decrease in estradiol. Combination therapy had no effect on plasma lipid and apolipoprotein B concns., but very-low-d. lipoprotein (VLDL) apolipoprotein B decreased, and apolipoprotein A-I concns. increased but A-II and phospholipids did not. These results suggest enhance lipoprotein lipase activity, consistent with the reciprocal changes in VLDL and LDL apolipoprotein B levels, apolipoprotein B enrichment of LDL particles, and increase in HDL cholesterol. The higher apolipoprotein A-I to A-II ratio indicates an increase in HDL2 subfraction due to inhibition of endothelial hepatic lipase, increased secretion of apolipoprotein A-I, or both. These effects are attributed to estradiol, which decreased less than after orchiectomy, and to addnl. adrenal androgen inhibition by flutamide. Thus, estradiol plays an important role in detg. plasma lipoprotein concns. in men, and androgens exert an antagonist effect. The lipoprotein profile resulting from the combination treatment is more beneficial than that resulting from orchiectomy or estrogen administration.

ACCESSION NUMBER: 1988:106709 CAPLUS
DOCUMENT NUMBER: 108:106709
TITLE: Changes in plasma lipoproteins during various androgen suppression therapies in men with prostatic carcinoma: effects of orchiectomy, estrogen, and combination treatment with **luteinizing hormone** -releasing **hormone** agonist and flutamide
AUTHOR(S): Moorjani, Sital; Dupont, Andre; Labrie, Fernand; Lupien, Paul J.; Gagne, Claude; Brun, Daniel; Giguere, Michel; Belanger, Alain; Cusan, Lionello
CORPORATE SOURCE: Res. Cent., Laval Univ. Hosp., Quebec City, PQ, Can.
SOURCE: J. Clin. Endocrinol. Metab. (**1988**), 66(2), 314-22
CODEN: JCEMAZ; ISSN: 0021-972X
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Changes in plasma lipoproteins during various androgen suppression therapies in men with prostatic carcinoma: effects of orchiectomy, estrogen, and combination treatment with **luteinizing hormone**-releasing **hormone** agonist and flutamide

SO J. Clin. Endocrinol. Metab. (**1988**), 66(2), 314-22
CODEN: JCEMAZ; ISSN: 0021-972X

AB Changes in plasma lipoproteins were studied in patients with **prostate cancer** during treatment with several androgen

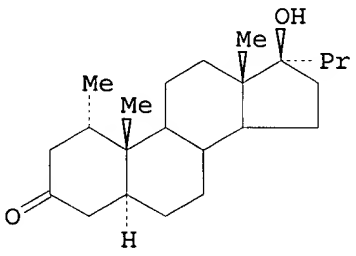
suppression therapies. Estrogen, orchiectomy, and a combination of **LH**-RH agonist and **antiandrogen** (flutamide) reduced plasma **testosterone** concns. (89-92%) and plasma estradiol decreased by 85, 44, and 54%, resp. Estrogen induced hypertriglyceridemia and elevation of plasma high-d. lipoprotein (HDL) cholesterol, phospholipid, and apolipoprotein A-I and A-II concns. Low-d. lipoprotein (LDL) cholesterol decreased but LDL apolipoprotein B did not. Apparently, the cardiovascular complications that occur during estrogen administration are not mediated through changes in lipoprotein profile, other than the hypertriglyceridemic effect. Orchiectomy caused hypercholesterolemia and an increase in both total and LDL apolipoprotein B, all of which are strong determinants of cardiovascular disease. The HDL concn. was not affected despite a redn. in plasma **testosterone**, perhaps due to a simultaneous decrease in estradiol. Combination therapy had no effect on plasma lipid and apolipoprotein B concns., but very-low-d. lipoprotein (VLDL) apolipoprotein B decreased, and apolipoprotein A-I concns. increased but A-II and phospholipids did not. These results suggest enhance lipoprotein lipase activity, consistent with the reciprocal changes in VLDL and LDL apolipoprotein B levels, apolipoprotein B enrichment of LDL particles, and increase in HDL cholesterol. The higher apolipoprotein A-I to A-II ratio indicates an increase in HDL2 subfraction due to inhibition of endothelial hepatic lipase, increased secretion of apolipoprotein A-I, or both. These effects are attributed to estradiol, which decreased less than after orchiectomy, and to addnl. adrenal androgen inhibition by flutamide. Thus, estradiol plays an important role in detg. plasma lipoprotein concns. in men, and androgens exert an antagonist effect. The lipoprotein profile resulting from the combination treatment is more beneficial than that resulting from orchiectomy or estrogen administration.

IT 13311-84-7, Flutamide
RL: BIOL (Biological study)
(androgen suppression by **LH**-RH and, lipoprotein profiles in men in)

IT 9034-40-6, **LH**-RH
RL: BIOL (Biological study)
(androgen suppression by flutamide and, lipoprotein profiles in men in)

L10 ANSWER 22 OF 30 CAPLUS COPYRIGHT 2001 ACS

GI



I

AB 17.alpha.-Propylmesterolone (I) [79243-67-7] was tested in the treatment of **acne**. Male and female patients applied a 3% alc. soln. of I twice daily on the face for a mean of 13 wk. Besides clin. controls with **acne** grading sebum excretion rate (SER) was detd. and the lipid fractions were sepd. before the onset of treatment, after 14 days, and

then monthly. Concomitantly, the levels of several hormones (serum **testosterone**, prolactin, FSH, **LH**, and estradiol) were detd. Clin. results were moderate to excellent in most of the patients. In 2 patients no therapy effects were apparent after 8 wk. SER was decreased in all patients to values 40-70% of pretreatment values. Sebaceous gland lipids and epidermal lipids were both effectively inhibited . Hormonal parameters showed no difference of pretreatment and posttreatment values. Pos. effects of a topical new **antiandrogen** were demonstrated for the 1st time. The interesting finding of decreased dermal and epidermal lipids suggests that not only sebaceous glands but also overstimulated epidermal structures may be inhibited by this **antiandrogen**.

ACCESSION NUMBER: 1987:149804 CAPLUS
DOCUMENT NUMBER: 106:149804
TITLE: Efficacy of topically applied 17.alpha.-propylmesterolone in acne patients
AUTHOR(S): Schmidt, J. B.; Spona, J.
CORPORATE SOURCE: 2nd Dep. Dermatol., Univ. Vienna, Vienna, A-1090, Austria
SOURCE: Endocrinol. Exp. (**1987**), 21(1), 71-8
CODEN: ENEXAM; ISSN: 0013-7200
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Endocrinol. Exp. (**1987**), 21(1), 71-8
CODEN: ENEXAM; ISSN: 0013-7200
AB 17.alpha.-Propylmesterolone (I) [79243-67-7] was tested in the treatment of **acne**. Male and female patients applied a 3% alc. soln. of I twice daily on the face for a mean of 13 wk. Besides clin. controls with **acne** grading sebum excretion rate (SER) was detd. and the lipid fractions were sepd. before the onset of treatment, after 14 days, and then monthly. Concomitantly, the levels of several hormones (serum **testosterone**, prolactin, FSH, **LH**, and estradiol) were detd. Clin. results were moderate to excellent in most of the patients. In 2 patients no therapy effects were apparent after 8 wk. SER was decreased in all patients to values 40-70% of pretreatment values. Sebaceous gland lipids and epidermal lipids were both effectively inhibited . Hormonal parameters showed no difference of pretreatment and posttreatment values. Pos. effects of a topical new **antiandrogen** were demonstrated for the 1st time. The interesting finding of decreased dermal and epidermal lipids suggests that not only sebaceous glands but also overstimulated epidermal structures may be inhibited by this **antiandrogen**.

L10 ANSWER 23 OF 30 CAPLUS COPYRIGHT 2001 ACS
AB At 1 or 8 days after treatment of intact rats with lutrelin [66866-63-5] (25 .mu.g) plus flutamide [13311-84-7] (3 or 10 mg), the serum levels of **testosterone** [58-22-0] and **LH** [9002-67-9] were elevated as compared to control rats; whereas, treatment with lutrelin plus cyproterone acetate [427-51-0] (3 or 10 mg) failed to increase serum **testosterone** or **LH** levels after 1, 8, or 21 days. At 21 days after treatment with flutamide plus lutrelin, the **testosterone** and **LH** levels were no longer elevated. Thus, in the treatment of **prostatic cancer**, combination of **antiandrogen**, of the cyproterone acetate-type with **LH**-RH agonists may be more useful than combinations contg. the pure antiandrogens of the flutamide type.
ACCESSION NUMBER: 1986:619062 CAPLUS
DOCUMENT NUMBER: 105:219062

TITLE: Short-term effects of the combination of an **LH** -RH-agonist with different antiandrogens on the hypothalamic-hypophyseal gonadal system of the intact male rat
AUTHOR(S): Habenicht, U. F.; El Etreby, M. F.; Neumann, F.
CORPORATE SOURCE: Res. Lab., Schering A.-G., Berlin, Fed. Rep. Ger.
SOURCE: Int. Congr. Ser. - Excerpta Med. (**1986**), 683(Endocrinology '85), 451-3
CODEN: EXMDA4; ISSN: 0531-5131
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Short-term effects of the combination of an **LH**-RH-agonist with different antiandrogens on the hypothalamic-hypophyseal gonadal system of the intact male rat
SO Int. Congr. Ser. - Excerpta Med. (**1986**), 683(Endocrinology '85), 451-3
CODEN: EXMDA4; ISSN: 0531-5131
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ST antiandrogen LHRH agonist **LH testosterone**; cyproterone LHRH agonist **LH testosterone**; flutamide LHRH agonist **LH testosterone**; lutrelin androgen inhibitor **LH testosterone**
IT Blood serum
(**LH** and **testosterone** of, antiandrogens and **LH**-RH agonists effect on)
IT Androgens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors, **LH** and **testosterone** of blood serum in response to **LH**-RH agonist and)
IT Endocrine system
(anterior pituitary-hypothalamus-testis, antiandrogens and **LH** -RH agonist effect on)
IT 427-51-0 13311-84-7
RL: BIOL (Biological study)
(**LH** and **testosterone** of blood serum in response to **LH**-RH agonist and)
IT 66866-63-5
RL: BIOL (Biological study)
(**LH** and **testosterone** of blood serum in response to antiandrogens and)
IT 58-22-0 9002-67-9
RL: BIOL (Biological study)
(of blood serum, antiandrogens and **LH**-RH agonist effect on)

L10 ANSWER 24 OF 30 CAPLUS COPYRIGHT 2001 ACS
AB Although orchiectomy, estrogens (DES [56-53-1]), and **LH**-RH agonists (buserelin [57982-77-1]) suppress testicular androgens, they are

without effect on adrenal androgens which are converted into dihydrotestosterone [521-18-6] in the prostate. It is therefore necessary to develop substances able to block the action of all androgens, whatever their source, on target organs. The non-steroid Anandron (RU 23908 [63612-50-0]), when administered orally, gives rise to a high and sustained plasma level of intact compd. that inhibits **testosterone** [58-22-0] binding to its receptor. This inhibition, however, occurs not only in the prostate but also in the pituitary. The neg. feedback action of androgens is thus inhibited by Anandron resulting in an increased secretion of **testosterone** and explaining the necessity of combining Anandron with castration (whether surgical or medical by an **LH**-RH agonist). Anandron opposes, on the one hand, the action of adrenal androgens and, on the one other, of the **testosterone** surge that occurs during the early days of treatment with the **LH** -RH analog. The efficacy of the combined treatment was demonstrated exptl. in rats.

ACCESSION NUMBER: 1986:400861 CAPLUS
DOCUMENT NUMBER: 105:861
TITLE: **Prostate cancer**: biological basis for the use of an **antiandrogen** in its treatment
AUTHOR(S): Raynaud, J. P.; Coussediere, D.; Moguilewsky, M.; Pottier, J.; Labrie, F.
CORPORATE SOURCE: Roussel-Uclaf, Paris, F 75007, Fr.
SOURCE: Bull. Cancer (**1986**), 73(1), 36-46
CODEN: BUCABS; ISSN: 0007-4551
DOCUMENT TYPE: Journal
LANGUAGE: French

TI **Prostate cancer**: biological basis for the use of an **antiandrogen** in its treatment

SO Bull. Cancer (**1986**), 73(1), 36-46
CODEN: BUCABS; ISSN: 0007-4551

AB Although orchiectomy, estrogens (DES [56-53-1]), and **LH**-RH agonists (buserelin [57982-77-1]) suppress testicular androgens, they are without effect on adrenal androgens which are converted into dihydrotestosterone [521-18-6] in the prostate. It is therefore necessary to develop substances able to block the action of all androgens, whatever their source, on target organs. The non-steroid Anandron (RU 23908 [63612-50-0]), when administered orally, gives rise to a high and sustained plasma level of intact compd. that inhibits **testosterone** [58-22-0] binding to its receptor. This inhibition, however, occurs not only in the prostate but also in the pituitary. The neg. feedback action of androgens is thus inhibited by Anandron resulting in an increased secretion of **testosterone** and explaining the necessity of combining Anandron with castration (whether surgical or medical by an **LH**-RH agonist). Anandron opposes, on the one hand, the action of adrenal androgens and, on the one other, of the **testosterone** surge that occurs during the early days of treatment with the **LH** -RH analog. The efficacy of the combined treatment was demonstrated exptl. in rats.

ST **antiandrogen** LHRH agonist **prostate cancer**

IT Adrenal cortex, metabolism
(androgen formation by, **antiandrogen** inhibition of, in **prostate cancer**)

IT Pituitary gland, anterior lobe
(androgen receptors of, **antiandrogen** effect on, in **prostate cancer**)

IT Neoplasm inhibitors

(antiandrogens and **LH**-RH agonists, in prostate gland)
IT Receptors
RL: BIOL (Biological study)
(for androgens, of pituitary gland and prostate gland, **antiandrogen** effect on, in **prostate cancer**)
IT Prostate gland
(neoplasm, treatment of, with antiandrogen and **LH**-RH agonist)
IT 58-22-0
RL: FORM (Formation, nonpreparative)
(formation of, **antiandrogen** and **LH**-RH agonists effect on, in **prostate cancer**)
IT 521-18-6
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metab. of, **antiandrogen** effect on, in **prostate cancer**)
IT 63612-50-0
RL: BIOL (Biological study)
(prostate cancer treatment with **LH**-RH agonists and)
IT 56-53-1 57982-77-1
RL: BIOL (Biological study)
(**prostate cancer** treatment with **antiandrogen** and)

L10 ANSWER 25 OF 30 CAPLUS COPYRIGHT 2001 ACS
AB The effects of a simultaneous administration of the antiandrogen flutamide [13311-84-7] and microcapsules of the agonist 6-D-tryptophan-**LH**-RH (D-Trp-6-**LH**-RH) [57773-63-4] were studied in the Dunning R-3327H rat prostate adenocarcinoma model to det. whether the combination of these 2 drugs might inhibit tumor growth more effectively than single agents. Microcapsules of D-Trp-6-**LH**-RH, calcd. to release a controlled dose of 25 .mu.g/day for a period of 30 days were injected i.m. once a month. Flutamide was administered s.c. at a daily dose of 25 mg/kg. The therapy was started 100 days after the tumor transplantation and continued for 60 days. Tumor wts. and vols. were significantly reduced in rats treated with microcapsules or flutamide alone, but the former drug inhibited tumor growth more than the latter. The combined treatment of flutamide and microcapsules decreased tumor wt. and vol., but did not exert a synergistic effect on tumor growth, the redn. being smaller for the combination than for the microcapsules alone. There was an elevation of serum **testosterone** [58-22-0], **LH** [9002-67-9], and prolactin [9002-62-4] in rats treated with flutamide. On the other hand, in rats given microcapsules of D-Trp-6-**LH**-RH, **testosterone** decreased to castration levels within 7 days and remained at nondetectable values, serum **LH** and prolactin levels being also suppressed in this group. The combined administration of microcapsules and flutamide also decreased serum **testosterone** to nondetectable levels by day 7 and suppressed serum **LH** and prolactin. The findings raise doubts of whether the daily administration of the combination of **LH**-RH agonist with an antiandrogen offers an advantage over the use of microcapsules of an agonist like D-Trp-6-**LH**-RH alone in the treatment of prostatic carcinoma.
ACCESSION NUMBER: 1985:465288 CAPLUS
DOCUMENT NUMBER: 103:65288
TITLE: Investigation of the combination of the agonist D-Trp-6-**LH**-RH and the **antiandrogen** flutamide in the treatment of Dunning R-3327H **prostate cancer** model
AUTHOR(S): Redding, Tommie W.; Schally, Andrew V.

CORPORATE SOURCE: VA Med. Cent., New Orleans, LA, 70146, USA
SOURCE: Prostate (N. Y.) (**1985**), 6(3), 219-32
CODEN: PRSTDS; ISSN: 0270-4137
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Investigation of the combination of the agonist D-Trp-6-**LH**-RH and the **antiandrogen** flutamide in the treatment of Dunning R-3327H **prostate cancer** model

SO Prostate (N. Y.) (**1985**), 6(3), 219-32
CODEN: PRSTDS; ISSN: 0270-4137

AB The effects of a simultaneous administration of the antiandrogen flutamide [13311-84-7] and microcapsules of the agonist 6-D-tryptophan-**LH**-RH (D-Trp-6-**LH**-RH) [57773-63-4] were studied in the Dunning R-3327H rat prostate adenocarcinoma model to det. whether the combination of these 2 drugs might inhibit tumor growth more effectively than single agents. Microcapsules of D-Trp-6-**LH**-RH, calcd. to release a controlled dose of 25 .mu.g/day for a period of 30 days were injected i.m. once a month. Flutamide was administered s.c. at a daily dose of 25 mg/kg. The therapy was started 100 days after the tumor transplantation and continued for 60 days. Tumor wts. and vols. were significantly reduced in rats treated with microcapsules or flutamide alone, but the former drug inhibited tumor growth more than the latter. The combined treatment of flutamide and microcapsules decreased tumor wt. and vol., but did not exert a synergistic effect on tumor growth, the redn. being smaller for the combination than for the microcapsules alone. There was an elevation of serum **testosterone** [58-22-0], **LH** [9002-67-9], and prolactin [9002-62-4] in rats treated with flutamide. On the other hand, in rats given microcapsules of D-Trp-6-**LH**-RH, **testosterone** decreased to castration levels within 7 days and remained at nondetectable values, serum **LH** and prolactin levels being also suppressed in this group. The combined administration of microcapsules and flutamide also decreased serum **testosterone** to nondetectable levels by day 7 and suppressed serum **LH** and prolactin. The findings raise doubts of whether the daily administration of the combination of **LH**-RH agonist with an antiandrogen offers an advantage over the use of microcapsules of an agonist like D-Trp-6-**LH**-RH alone in the treatment of prostatic carcinoma.

IT Blood serum
(**LH** and prolactin and **testosterone** of, in prostate gland adenocarcinoma, flutamide and **LH**-RH analog effect on)

IT Androgens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors, prostate adenocarcinoma treatment with **LH**-RH analog and)

IT Neoplasm inhibitors
(adenocarcinoma, flutamide and **LH**-RH analog as, in prostate gland)

IT Prostate gland
(neoplasm, adenocarcinoma, treatment of, with flutamide and **LH**-RH analog)

IT 58-22-0 9002-62-4, biological studies 9002-67-9
RL: BIOL (Biological study)
(of blood serum, in prostate gland adenocarcinoma, flutamide and **LH**-RH analog effect on)

IT 13311-84-7
RL: BIOL (Biological study)
(prostate gland adenocarcinoma treatment with **LH**-RH analog and)

L10 ANSWER 26 OF 30 CAPLUS COPYRIGHT 2001 ACS

AB Complete withdrawal of androgens by use of an **LH**-RH agonist and an antiandrogen (or castration and an antiandrogen) produced a pos. response in >95% of patients with prostatic carcinoma. Treatment with HOE 766 [57982-77-1] and RU 23908 [63612-50-0] or castration plus **LH** -RH agonist normalized serum prostate acid phosphatase (PAP) [9001-77-8] levels in the majority of patients. In patients showing a relapse after DES [56-53-1] or castration therapy, however, the antiandrogen plus **LH**-RH agonist regimen was much less effective. Administration of antiandrogen and **LH**-RH agonist decreased serum **testosterone** [58-22-0], dehydroepiandrosterone [53-43-0], and dehydroepiandrosterone sulfate [651-48-9], whereas serum cortisol [50-23-7] was unchanged. Serum **LH** [9002-67-9] levels were also unchanged by this regimen but serum **LH** bioactivity decreased, suggesting that a loss of **LH** bioactivity and not testicular desensitization caused the inhibition of steroidogenesis during **LH** -RH agonist therapy. Treatment with **LH**-RH agonist and antiandrogen had no effect on blood indexes, but some side effects typical of climacteric and hypoandrogenicity were experienced. These results are accompanied by a review of the literature on testicular function inhibition by **LH**-RH agonists.

ACCESSION NUMBER: 1984:564017 CAPLUS
DOCUMENT NUMBER: 101:164017
TITLE: Medical castration in men: the first clinical application of **LH**-RH agonists
AUTHOR(S): Labrie, F.; Belanger, A.; Dupont, A.; St-Arnaud, R.
CORPORATE SOURCE: Med. Cent., Laval Univ., Quebec, PQ, G1V 4G2, Can.
SOURCE: Fertil. Steril., Proc. World Congr., 11th (**1984**), Meeting Date 1983, 25-39. Editor(s): Harrison, Robert Frederick; Bonnar, John; Thompson, William. MTP: Lancaster, UK.
CODEN: 52DUAI
DOCUMENT TYPE: Conference
LANGUAGE: English

TI Medical castration in men: the first clinical application of **LH** -RH agonists

SO Fertil. Steril., Proc. World Congr., 11th (**1984**), Meeting Date 1983, 25-39. Editor(s): Harrison, Robert Frederick; Bonnar, John; Thompson, William. Publisher: MTP, Lancaster, UK.
CODEN: 52DUAI

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of climacteric and hypoandrogenicity were experienced. These results are accompanied by a review of the literature on testicular function inhibition by **LH**-RH agonists.

ST LHRH agonist **antiandrogen prostate cancer**; sex hormone serum LHRH agonist **antiandrogen**; castration **antiandrogen prostate cancer**; testis function LHRH agonist

IT Testis
(function of, **LH**-RH agonists effect on, in men)

IT Blood serum
(hormones and prostatic acid phosphatase of, antiandrogen and **LH**-RH agonists effect on, in prostate carcinoma in men)

IT Blood
(indexes of, antiandrogen and **LH**-RH agonist effect on, in prostate carcinoma in men)

IT Androgens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors, prostate carcinoma response to **LH**-RH agonists and, in men)

IT Carcinoma
(of prostate gland, treatment of, with antiandrogen and **LH**-RH agonists, in men)

IT Prostate gland
(neoplasm, carcinoma, treatment of, with antiandrogen and **LH**-RH agonists, in men)

IT Hormones
RL: BIOL (Biological study)
(sex, of blood serum, antiandrogen and **LH**-RH agonists effect on, in prostate carcinoma in men)

IT 50-23-7 53-43-0 58-22-0 651-48-9 9002-67-9
RL: BIOL (Biological study)
(of blood serum, antiandrogen and **LH**-RH agonists effect on, in prostate carcinoma in men)

IT 9001-77-8
RL: BIOL (Biological study)
(of prostate gland in, blood serum, antiandrogen and **LH**-RH agonists effect on)

IT 63612-50-0
RL: BIOL (Biological study)
(prostate carcinoma treatment with **LH**-RH agonists and, in men)

IT 56-53-1
RL: BIOL (Biological study)
(prostate carcinoma treatment with, in men, antiandrogen and **LH**-RH agonists in relation to)

L10 ANSWER 27 OF 30 CAPLUS COPYRIGHT 2001 ACS

AB Although castration levels of serum androgens are consistently achieved after 2-3 wk of treatment with **LH**-RH [9034-40-6] agonists, the administration of these peptides alone in adult men is always accompanied by a transient increase in plasma **testosterone** [58-22-0] and dihydrotestosterone [521-18-6] levels, which last for 5-15 days at the beginning of treatment, and is accompanied by disease flare-up in some cases, thus seriously limiting the acceptability of this otherwise efficient and well-tolerated treatment. The simultaneous administration of a pure **antiandrogen** neutralized the influence of the transient increase in serum androgens on **prostate cancer**, as indicated by the 60% decrease in serum prostatic acid phosphatase

[9001-77-8] obsd. within 5 days of combined treatment with an **LH** -RH agonist Buserelin [57982-77-1] and a pure **antiandrogen** Anandron [63612-50-0]. The addn. of a pure **antiandrogen** thus makes fully acceptable the use of **LH**-RH agonists as an advantageous substitute for surgical castration and estrogens in the treatment of **prostate cancer**.

ACCESSION NUMBER: 1984:466370 CAPLUS
DOCUMENT NUMBER: 101:66370
TITLE: Simultaneous administration of pure antiandrogens, a combination necessary for the use of **luteinizing hormone**-releasing **hormone** agonists in the treatment of prostate cancer
AUTHOR(S): Labrie, Fernand; Dupont, Andre; Belanger, Alain; Emond, Jean; Monfette, Gerard
CORPORATE SOURCE: Le Cent. Hosp., Univ. Laval, Quebec, PQ, G1V 4G2, Can.
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (**1984**), 81(12), 3861-3
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Simultaneous administration of pure antiandrogens, a combination necessary for the use of **luteinizing hormone**-releasing **hormone** agonists in the treatment of prostate cancer

SO Proc. Natl. Acad. Sci. U. S. A. (**1984**), 81(12), 3861-3
CODEN: PNASA6; ISSN: 0027-8424

AB Although castration levels of serum androgens are consistently achieved after 2-3 wk of treatment with **LH**-RH [9034-40-6] agonists, the administration of these peptides alone in adult men is always accompanied by a transient increase in plasma **testosterone** [58-22-0] and dihydrotestosterone [521-18-6] levels, which last for 5-15 days at the beginning of treatment, and is accompanied by disease flare-up in some cases, thus seriously limiting the acceptability of this otherwise efficient and well-tolerated treatment. The simultaneous administration of a pure **antiandrogen** neutralized the influence of the transient increase in serum androgens on **prostate cancer** , as indicated by the 60% decrease in serum prostatic acid phosphatase [9001-77-8] obsd. within 5 days of combined treatment with an **LH** -RH agonist Buserelin [57982-77-1] and a pure **antiandrogen** Anandron [63612-50-0]. The addn. of a pure **antiandrogen** thus makes fully acceptable the use of **LH**-RH agonists as an advantageous substitute for surgical castration and estrogens in the treatment of **prostate cancer**.

IT Blood plasma
(acid phosphatase and dihydrotestosterone and **testosterone** of, in prostate cancer in men, antiandrogens and **LH**-RH agonists effect on)

IT Androgens
RL: BIOL (Biological study)
(antagonists, prostate cancer treatment with **LH**-RH agonists and, in men)

IT Prostate gland
(neoplasm, adenocarcinoma, antiandrogens and **LH**-RH agonists in treatment of, in men)

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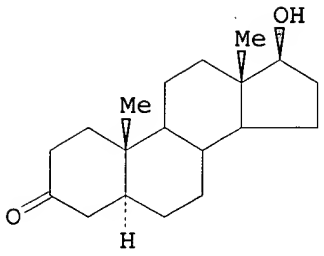
GI



IV

AB Tamoxifen (I) (40 mg/day) (an antiestrogen), cyproterone acetate (II) (100 mg/day) (an **antiandrogen**), or bromocriptine (III) (doses increasing from 2.5 to 15 mg/day over 6 wk) (a prolactin [9002-62-4] inhibitor) was given to men with **benign prostatic hyperplasia**. Prostate gland biopsies from I-treated men showed no increase or decrease in prostate muscle cell organelles, whereas the no. of organelles related to smooth muscle cell cytoplasm was decreased 28% by II and was increased 57% by III. In men treated with I, there was an increase in blood gonadotropins, and in 2 of 5 men there was a slight increase in blood **testosterone** [58-22-0]. In the III-treated group, there were no alterations in blood **testosterone** **LH** [9002-67-9], FSH [9002-68-0], or 17.beta.-estradiol [50-28-2], whereas prolactin was decreased. In the II-treated group, the gonadotropin and **testosterone** levels were decreased. II decreased the endogenous 5.alpha.-dihydrotestosterone (IV) [521-18-6] level in prostate tissue, whereas I and III had no such effect. None of the treatments altered the endogenous prostate levels of estrone [53-16-7], estradiol, or estriol [50-27-1]. The relations of stromal growth and hormones in **benign prostatic hyperplasia** are reviewed.

ACCESSION NUMBER: 1983:552397 CAPLUS
DOCUMENT NUMBER: 99:152397
TITLE: Correlative morphological and biochemical investigations on the stromal tissue of the human prostate
AUTHOR(S): Bartsch, G.; Daxenbichler, G.; Rohr, H. P.
CORPORATE SOURCE: Dep. urol., Univ. Innsbruck, Austria
SOURCE: J. Steroid Biochem. (**1983**), 19(1A), 147-54
CODEN: JSTBBK; ISSN: 0022-4731
DOCUMENT TYPE: Journal
LANGUAGE: English

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CODEN: JSTBBK; ISSN: 0022-4731
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L10 ANSWER 29 OF 30 CAPLUS COPYRIGHT 2001 ACS

AB At doses which have no or minimal inhibitory effect when administered alone, the **LH**-RH agonist HOE-766 [57982-77-1] and the **antiandrogen** RU-23908 [63612-50-0] administered simultaneously cause a marked inhibition of ventral prostate and seminal vesicle wt. after 5 mo of treatment. The effect of the **LH**-RH agonist is due to a blockage of the testicular steroidogenic pathway. The same **LH**-RH agonist administered to adult men with **cancer** of the **prostate** causes a marked decrease of serum **testosterone** [58-22-0] and dihydrotestosterone [521-18-6] to castration levels within 1-2 wk. Administration of the pure **antiandrogen** to men with **cancer** of the **prostate** already receiving the **LH**-RH agonist does not interfere with the **LH**-RH agonist-induced blockage of androgen biosynthesis. Moreover, objective signs of remission of the disease are rapidly obsd. in 8 of 10 patients. The ease of application of this new form of hormonal therapy which neutralizes androgens from all sources should facilitate its early administration and thus minimize the development of metastases and androgen-resistant cell clones.

ACCESSION NUMBER: 1983:534104 CAPLUS
DOCUMENT NUMBER: 99:134104
TITLE: New hormonal treatment in **cancer** of the **prostate**: combined administration of an **LH**-RH agonist and an **antiandrogen**
AUTHOR(S): Labrie, F.; Dupont, A.; Belanger, A.; Lefebvre, F. A.; Cusan, L.; Monfette, G.; Laberge, J. G.; Emond, J. P.; Raynaud, J. P.; et al.
CORPORATE SOURCE: Dep. Mol. Endocrinol., Cent. Hosp. Univ. Laval, PQ, G1V 4G2, Can.
SOURCE: J. Steroid Biochem. (**1983**), 19(1C), 999-1007
CODEN: JSTBBK; ISSN: 0022-4731
DOCUMENT TYPE: Journal
LANGUAGE: English

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CODEN: JSTBBK; ISSN: 0022-4731

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ST **prostate cancer** LHRH **antiandrogen**; **testosterone** HOE 766 **prostate cancer**; dihydrotestosteone HOE 766 **prostate cancer**; HOE 766 **prostate cancer** therapy; RU 23908 **prostate cancer** therapy

L10 ANSWER 30 OF 30 CAPLUS COPYRIGHT 2001 ACS

AB Flutamide (I) [13311-84-7], a nonsteroidal **antiandrogen**, was given to 11 men with **prostate cancer**, in doses of 750-1500 mg daily for 0.5-7 mo. Four patients had a clin. remission and 7 showed no response. All the patients showed a profound change in the peripheral metab. of **testosterone** [58-22-0]: markedly increased conversion to androsterone [53-41-8] and correspondingly decreased conversion to etiocholanolone [53-42-9]; the androsterone-to-etiocholanolone ratio rose to levels never before obsd. consistently in any group of healthy or diseased humans. This change was probably due to alteration by I of the relative activities of steroid 5.alpha.- and 5.beta.-reductase in favor of the former. Twenty-four-h mean plasma **testosterone** was increased in 5 of the 6 patients studied for this parameter; for the group as a whole, **testosterone** rose from 279 to 484 ng/dL. Twenty-four-h mean values for plasma dihydrotestosterone [521-18-6], dehydroisoandrosterone [53-43-0], **LH** [9002-67-9], and FSH [9002-68-0] showed no significant change, for the group as a whole, in the same 6 patients. Since I did not change the metabolic clearance rate or vol. of distribution of **testosterone** tracers, the increased plasma levels of the hormone were probably due to increased prodn.

ACCESSION NUMBER: 1978:115413 CAPLUS
DOCUMENT NUMBER: 88:115413
TITLE: The effect of flutamide on **testosterone** metabolism and the plasma levels of androgens and gonadotropins
AUTHOR(S): Hellman, Leon; Bradlow, H. L.; Freed, S.; Levin, J.; Rosenfeld, R. S.; Whitmore, W. F.; Zumoff, Barnett
CORPORATE SOURCE: Dep. Oncol., Montefiore Hosp. Med. Cent., Bronx, N. Y., USA
SOURCE: J. Clin. Endocrinol. Metab. (**1977**), 45(6), 1224-9
CODEN: JCEMAZ; ISSN: 0021-972X
DOCUMENT TYPE: Journal
LANGUAGE: English

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SO J. Clin. Endocrinol. Metab. (**1977**), 45(6), 1224-9
CODEN: JCEMAZ; ISSN: 0021-972X

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ST flutamide **testosterone** metab cancer; prostate cancer flutamide **testosterone**; androgen metab flutamide cancer; gonadotropin metab flutamide cancer

IT 53-41-8 53-42-9
RL: BIOL (Biological study)
(as **testosterone** metabolite, flutamide effect on, in prostate cancer)